

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**
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Introduction

The mature placenta is composed of four distinct units of structure-function:

1. Chorionic plate and its contiguous vascularized fetal connective tissue
2. Interhemal villous trophoblast and the adjacent intervillous space
3. Basal plate and the underlying maternal uterine vasculature and decidua
4. Tripartite placental membranes consisting of amnion, chorion, and decidua

The chorionic plate (or fetal surface) consists of the fibrous connective tissue supporting the large muscular arteries and veins that distribute fetal blood flow from the umbilical cord to a family of 20-30 large villous trees(1, 2). The umbilical cord is a squamous epithelial lined conduit normally measuring between 40-80 cm at term that conducts fetal blood from the umbilicus to some location on the chorionic plate (or occasionally to the adjacent placental membranes). It contains paired arteries that spiral around a central vein; all surrounded by a hyaluronate rich matrix (Wharton's jelly) which provides considerable protection from external compression. The two arteries are connected at or just before their insertion site into the chorionic plate by an interarterial anastomosis (Hyrtl's anastomosis). Villous trees emanating from the underside of the chorionic plate branch multiple times as they conduct fetal blood through a succession of smaller arteries and veins until they reach capillaries that abut the trophoblastic interhemal membrane in the terminal villi. These conducting villi are sometimes referred to as primary, secondary, and tertiary stem villi with the last representing the arteriolar level at which blood flow to the gas exchanging terminal villi is ultimately regulated. The two critical anatomic features that must be maintained in this compartment are patency of the large villous vessels and short diffusion distance between capillaries and interhemal villous trophoblast.

Interhemal villous trophoblast consists of a single multinucleated layer of differentiated syncytiotrophoblast with underlying basement membrane and occasional basally located cytotrophoblast stem cells. Each stem cell is the progenitor for 80-100 fused syncytiotrophoblastic cells and these large syncytial sheets form a mosaic covering the entirety of the villous tree(3). Turnover of syncytiotrophoblast occurs via clustering of nuclei in syncytial knots followed by apoptosis and shedding into the maternal circulation(4). Critical features in this compartment are cellular viability, appropriate maturation in terms of endocrine, transport, anticoagulant, and immunoprotective function, and accessibility to maternal blood flow - meaning absence of adherent fibrin or inflammatory exudate.

The basal plate consists of 80-100 anchoring villi, a similar number of perpendicularly oriented perforating maternal arteries, and tangentially oriented draining maternal veins. Uniting these elements into a coherent anatomic structure is intermediate trophoblast, which arises from cytotrophoblast stem cells on the underside of the anchoring villi. This tissue invasive cell type elaborates large amounts of fibronectin-rich extracellular matrix, which constitutes a large portion of the basal plate and provides structural integrity. Closely related endovascular trophoblast is normally present throughout the wall of basal plate arteries and on the placental aspect of the large maternal veins. Important features of this compartment are appropriate remodeling of maternal vessels and sufficient depth and extent of interstitial implantation to resist premature separation.

The placental membranes at first glance appear distinct from the first three compartments. While this is certainly true in terms of function the anatomic differences are minor. The membranes form by involution of the placenta and retain all of its layers. The fetal surface of the membranes is covered by amnion and consists of chorionic connective tissue and occasional chorionic villi, albeit without fetal blood vessels. The villous trophoblast coalesces as the intervillous space is obliterated to form a third distinct morphologic variant of trophoblast known as chorion laeve or epithelioid trophoblast. This noninvasive trophoblast layer is supported by underlying maternal decidua, which lacks the remodeling seen in the

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**

Raymond W. Redline, MD

basal plate. Critical requirements for this compartment include the integrity and contiguity of all layers. In particular chorionic prostaglandin dehydrogenase in chorion laevae trophoblast must be functionally active and spatially positioned to inactivate labor-inducing prostaglandins elaborated from other layers, particularly the amnion(5, 6).

Group1: Chorioamnionitis

Background: The products of conception develop in the normally sterile uterine cavity. Parturition, however, requires an outlet to the external environment. This outlet, the cervicovaginal tract, like most other body orifices has a rich and complex microbial flora that can include aerobic and anaerobic bacteria, mycoplasma, and fungi. This environment can also transiently harbor organisms with a particular capacity to spread to and infect the products of conception. These include group B streptococci, *Listeria monocytogenes*, and the predominantly anaerobic flora associated with bacterial vaginosis. Contact between the gestational sac to the cervicovaginal tract does not occur until about 18-19 weeks gestation(7). After that time the secretory immune system and structural integrity of the cervix, the ineffective nature of uterine contractions prior to parturition, and the integrity of the placental membranes serve to protect the fetoplacental unit from ascending infection. Failure of one or more of these mechanisms may allow organisms to enter the endometrium or amniotic fluid. Antibacterial responses at these latter sites are handicapped by local immunosuppressive mechanisms, fetal immunologic immaturity, and the closed nature of the fetoplacental unit. The inflammatory response to ascending infection consists of an acute inflammatory neutrophilic infiltrate composed of maternal neutrophils from the intervillous circulation and small venules in the membranous decidua(8, 9). In many cases this maternal response is supplemented by a fetal response composed of neutrophils emanating from large vessels of the umbilical cord and chorionic plate. This localization of the inflammatory response reflects the site of infection with both maternal and fetal neutrophils migrating toward the amniotic cavity through chorion and amnion after leaving their respective circulations (acute chorioamnionitis). While the majority of amniotic fluid infections occur via the ascending route, other mechanisms of spread including hematogenous spread from other colonized body sites, contiguous spread from other pelvic organs, and direct inoculation of organisms during diagnostic procedures such as amniocentesis also occur.

Pathology: Acute chorioamnionitis should be separated into two components, the maternal and fetal inflammatory responses. Each of these in turn should be characterized in terms of its spatiotemporal progression (stage) and severity (grade)(10). The stages of maternal infection are (1) acute subchorionitis (neutrophils restricted to subchorionic fibrin and the membranous decidual-chorionic interface), (2) acute chorioamnionitis (neutrophils in chorion and amnion), and (3) necrotizing chorioamnionitis (signs of amnion necrosis). These signs include karyorrhexis of neutrophils, desquamation of amniotic epithelial cells, and bandlike eosinophilia of the amniotic basement membrane. The stages of fetal infection are (1) neutrophils in chorionic vessels (chorionic vasculitis) and/or umbilical vein (umbilical phlebitis), (2) umbilical arterial neutrophils (umbilical arteritis), and (3) neutrophils and neutrophilic debris forming arcs around umbilical vessels in the Wharton's jelly (necrotizing funisitis). Severe maternal responses are characterized by large accumulations of neutrophils (microabscesses) under the chorion(11). Severe fetal responses are characterized by near confluent neutrophilic infiltrates in the amniotic side of chorionic vessels with attenuation and degenerative changes of the vessel wall (intense chorionic vasculitis). Severe fetal responses may in some cases lead to mural thrombi in affected vessels.

Clinical Correlation: The incidence of histologic chorioamnionitis is inversely proportional to gestational age reaching over 50% below 28 weeks(12, 13). While in some cases infection may be a secondary consequence of prolonged membrane rupture in some cases, it is believed that placental infection plays a primary role in most extremely low birth weight preterm births (<32 weeks). Bacterial vaginosis is one risk factor for these infections(14). Spread of organisms from the infected placenta to the fetus (so-called early onset sepsis) is rare and chorioamnionitis is rarely a direct cause of intrauterine fetal death. One exception is untreated group B streptococcal infection, which is associated with a higher, but still limited risk of fetal infection. In general the ability to effectively eradicate intrauterine infections is limited and preterm delivery is inevitable. Recently, the fetal response to amniotic fluid infection has received special attention (fetal inflammatory response syndrome). It is currently believed

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**
Raymond W. Redline, MD

that various aspects of this response including circulating cytokines, bacterial toxins, and activation of the coagulation cascade predispose to cerebral palsy and other forms of neurologic impairment(15-17). A role for fetal inflammatory response syndrome in the development of chronic lung disease has also been proposed with conflicting evidence(18-20).

Group 2: Meconium Effects

Background: Acute episodes of in utero hypoxia, regardless of duration, can trigger redistribution of blood flow resulting in the release of fetal stool (meconium) into the amniotic fluid(21). This vagally-mediated reflex is believed to represent an adaptation preserving adequate perfusion to more critical vascular beds such as the central nervous and cardiovascular systems. In most cases the hypoxic episodes are brief and caused by transient umbilical cord occlusion which is common after 39 weeks as the fetus continues to grow and move in the face of decreases in the volumes of amniotic fluid and umbilical cord Wharton's jelly. Meconium is composed of large amounts of bile acid and phospholipases that can have direct caustic effects on fetal and placental tissues. Particularly important are effects on umbilical and chorionic blood vessels(22). The amount of meconium passed and the volume of fluid available to suspend it are important variables in determining its toxic effects. Probably of greater importance is duration of exposure since meconium diffuses relatively slowly through fetoplacental tissues. Prolonged duration of exposure is also important insofar as it is an indicator of a hypoxic event occurring prior to labor and delivery. Finally, meconium also appears to increase the risk for chorioamnionitis by several mechanisms including neutralization of bacterial inhibitory factors in amniotic fluid and direct chemotactic properties(23). Prolonged meconium exposure and severe fetal chorioamnionitis may also synergize to cause chorionic vessel injury.

Pathology: Pathologists play an important role in determining the presence and timing of meconium exposure. Meconium is a fine particulate red-brown pigment generally found within the vacuolated cytoplasm of tissue macrophages. It can be distinguished from hemosiderin and other pigments by clinical history of green stained fluid, its occurrence at term, negativity by iron stain, and its associated tissue changes. These latter include dehiscence and necrosis of amniocytes, amniotic connective tissue edema, and accumulation of tissue macrophages. Estimating duration of meconium exposure is an inexact science(24). It is believed that pigment appears in amnion approximately one hour after release. Spread to the membranous decidua takes at least three hours. Significant accumulations of pigment-laden macrophages in the deeper layers of the chorionic plate and Wharton's jelly, and green staining of the umbilical cord probably take at least 12-16 hours. A rare and clinically significant lesion associated with prolonged meconium exposure is meconium associated vascular necrosis(25). This lesion is characterized by apoptotic cell death of peripheral myocytes in the umbilical and chorionic vessels and has been associated with adverse outcome(26, 27).

Clinical Correlation: Meconium passage occurs in approximately 14% of all deliveries and is almost exclusively seen after 34 weeks gestation. While statistically associated with obstetric and neonatal complications it is neither a specific nor a sensitive indicator for them. Its predictive value in any given case is low. Amongst pathologic lesions, only meconium associated vascular necrosis has been associated with cerebral palsy and other adverse neurologic outcomes(28). The meconium aspiration syndrome is defined as respiratory distress requiring oxygen therapy associated with meconium release and an abnormal chest X ray(29). It has been associated with serious respiratory and neurologic complications and a significant mortality rate. It occurs in 11% of meconium-stained infants and has been correlated with the presence of meconium below the vocal cords. However, prompt suctioning of meconium from the airways after delivery has not made a major impact on morbidity and mortality(30). Current thinking suggests that adverse consequences of meconium aspiration syndrome are due to both direct effects of the meconium in the lung and the significant perinatal stresses that lead to deep aspiration of the meconium prior to birth.

Group 3: Maternal Vascular Underperfusion

Background: Chronic maternal underperfusion of the intervillous space can result from a variety of causes including underlying cardiac insufficiency, failure to expand intravascular volume during pregnancy, or structural abnormalities in arteries supplying the uterus. It is currently believed that the

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**

Raymond W. Redline, MD

major process leading to underperfusion is failure of trophoblast to appropriately invade and remodel the uterine spiral arteries. While the exact sequence or sequences of events leading to this outcome have not yet been worked out a number of contributing factors have been identified. These include initial exposure to fetoplacental antigens in first pregnancies, inherited polymorphisms in genes of the renin-angiotensin system, circulating anti-endothelial cell antibodies, and underlying uterine small vessel disease(31-34). The common denominator for all of these factors seems to be decreased oxygen delivery to the implantation site resulting in impaired trophoblast differentiation and inadequate placentation. In the absence of arterial remodeling, the placenta is chronically underperfused leading to decreased fetoplacental growth and, in some cases, release of vasoactive mediators in late pregnancy leading to the clinical syndrome of preeclampsia.

Pathology: Placentas affected by maternal underperfusion generally show multiple abnormalities that together allow a specific diagnosis to be rendered(35). One important, often overlooked, feature is decreased weight for gestational age and decreased placental weight relative to that of the infant (increased fetoplacental weight ratio)(36, 37). In severe cases this correlates with late impairment of placental growth (distal villous hypoplasia) as the fetus sacrifices placental perfusion in order to supply critical vascular beds such as the central nervous and cardiovascular systems(38, 39). Also common in severe cases are villous infarcts caused by thrombosis of abnormal maternal arteries and a thin umbilical cord resulting from extracellular volume depletion and decreased hydration of Wharton's jelly(40, 41). Lesser degrees or durations of underperfusion and hypoxia can lead to stasis with intervillous fibrin deposition, accelerated syncytiotrophoblast turnover with increased syncytial knots, and ischemia leading to foci of villous agglutination(42-44). Finally, there are other findings directly reflecting inadequate placentation. These include persistent muscularization of basal plate arteries, aggregates of immature or prematurely differentiated (placental site giant cells or epithelioid (chorion laeve type) trophoblast in the basal plate), and medial hypertrophy or fibrinoid necrosis (acute atherosclerosis) of maternal arterioles in the membranous decidua(45, 46).

Clinical Correlation: Chronically underperfused placentas are associated with fetal growth restriction, premature birth owing to either premature labor or premature rupture of membranes, premature placental separation (abruptio placenta), and an increased risk for the development of preeclampsia(47-50). Clinical conditions predisposing to maternal underperfusion include type I diabetes mellitus, connective tissue disease, chronic renal insufficiency, essential hypertension, and underlying maternal coagulopathies including thrombophilic mutations and antiphospholipid syndrome(51). Familial aggregation of preeclampsia and underlying maternal vascular disease may at least in part be due inheritance of the so-called metabolic syndrome characterized by abnormal serum lipid levels, enhanced production of acute phase inflammatory mediators, and a predisposition to vascular damage related to reactive oxygen intermediates. These patients are often obese and predisposed to developing obesity, type II diabetes, sleep apnea, and hypertension in later life.

Group 4: Retroplacental Hemorrhage (Abruptio)

1. Acute Abruptio Placenta

Background: Abruptio placenta (placental abruption), the sudden separation of a significant portion of the placenta from its underlying maternal blood supply prior to delivery, is one important cause of acute hypoxic injury. While separation can occur at any location, clinically significant abruptions tend to occur in the central part of the disc and to involve uterine arteries rather than veins. Loss of arterial integrity can usually often be attributed to one of three mechanisms: (1) underlying disease in the vessel wall (e.g. preeclampsia and related disorders of implantation), (2) physical force (increased intraluminal pressure or external shear forces associated with trauma), and (3) ischemia-reperfusion following vasospasm (e.g. substance abuse involving cocaine or other vasoactive drugs such as nicotine)(50, 52, 53). Other local processes leading to acute uteroplacental separation include cervical dilation with placenta previa and uterine rupture with attempted vaginal delivery following a previous C-section.

Pathology: It is often stated that the correlation between pathologic and clinical abruption is poor(54). Indeed vaginal bleeding followed by immediate delivery can occur in the absence of placental lesions. Likewise, clinical signs and symptoms of abruption may also prove unreliable. The gold

AP103 Placental Pathology: Keeping It Simple and Focusing on What Matters

Raymond W. Redline, MD

standard for diagnosis of abruptio placenta is direct visualization of retroplacental hemorrhage at the time of C-section. Nevertheless, most placentas in cases of abruptio placenta show one or more of a cluster of findings that allow a diagnosis of findings consistent with abruption to be made with some confidence. The best pathologic evidence is a finding of a retroplacental hematoma with either placental indentation or intraplacental extension. In the absence of these findings, microscopic evidence of interstitial hemorrhage in the basal plate or diffuse retromembranous hemorrhage is helpful. Ischemic changes in the overlying placenta such as recent villous infarction or villous stromal hemorrhage are also very suggestive of abruption(55). Finally, lesions associated with chronic maternal underperfusion, as listed above, are very commonly associated with abruption and can help strengthen a strong clinical suspicion of the diagnosis(56).

Clinical Correlation: The classical clinical signs of abruptio placenta include vaginal bleeding, abdominal pain, and uterine rigidity. Abruption is associated with a number of adverse outcomes including preterm delivery, fetal growth restriction, stillbirth, and hypoxic ischemic encephalopathy(57, 58). As noted above hypertension, maternal substance abuse, advanced maternal age, low pregnancy weight gain, grand multiparity, and strenuous physical labor are known predisposing risk factors. Patients with evidence of early pregnancy bleeding, i.e. chronic abruption (see above) are also at risk for later acute abruption. A subgroup of patients has repetitive abruptions and both inherited and acquired maternal coagulation disorders may play a role in some of these patients(59-61).

2. Chronic Marginal Abruption

Background: Lateral growth of the placenta involves remodeling of large uterine veins(62). These large obliquely oriented structures may rupture prematurely if poorly supported by the surrounding endometrium or subjected to elevated intramural pressure due to obstruction of larger upstream veins such as the vena cava(63, 64). Unlike arterial rupture resulting in abruptio placenta, venous hemorrhage tends to occur at the placental margins and to escape at lower pressure(65). For these reasons, marginal separation may not result in immediate delivery instead presenting as threatened abortion in early pregnancy or chronic abruption in later pregnancy. Factors that have been associated with chronic abruption include multiparity, smoking, oligohydramnios, and excessively deep uterine implantation(66, 67).

Pathology: Chronic abruption, like maternal underperfusion, is associated with a cluster of placental findings. These include old marginal blood clot, circumvallate membrane insertion, chorioamniotic hemosiderin deposition, and green (biliverdin) staining of the fetal surface(68). Circumvallation may develop as a consequence of blood accumulating in the space between the decidua and chorion leading to undermining or folding of the marginal chorionic plate. When circumvallation is attributable to chronic marginal separation, old blood clot and local hemosiderin deposition are seen on histologic sections. Hemosiderin stains blue by iron stain, but other hemoglobin related pigments do not. Any pigment seen in a premature placenta favors chronic abruption rather than meconium release which is extremely uncommon before 37 weeks.

Clinical Correlation: Chronic abruption is often associated with oligohydramnios in a syndrome known as the chronic abruption-oligohydramnios sequence(69). These chronic marginal hemorrhages are often detected by ultrasound as so-called subchorionic hemorrhages(70). Serial ultrasound studies have documented the development of circumvallation following repeated subchorionic hemorrhages(71). Chronic abruption is an important cause of preterm delivery and may be associated with an atypical form of neonatal lung disease. It is also a significant risk factor for cerebral palsy and other forms of neurologic impairment in term infants(72).

Group 5: Chronic Villitis

1. Infectious

Background: Although ascending infections caused by organisms from the cervicovaginal tract can occur in the second trimester, most congenital infections in the first half of pregnancy are acquired hematogenously(73). The majority is the result of primary infection, since previous exposure usually

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**

Raymond W. Redline, MD

elicits protective antibodies in the mother. Routine bacterial and fungal infections are rare. Spirochetes (*T pallidum*, *B burgdorferi*), parasites (*T gondii*, *T cruzi*, *P falciparum*, *S hematobium*), and viruses (cytomegalovirus, varicella zoster virus, herpes simplex virus, rubella virus, poxviruses, parvovirus B19, enteroviruses, HIV, Hepatitis B and C) are the major causative agents. Organisms may lodge and elicit inflammation in the intervillous space (*P falciparum*, *B burgdorferi*, *S hematobium*), cross the placenta without eliciting an inflammatory response (Parvovirus B19, HIV, Hepatitis B and C, most enteroviruses), or infect both placenta and fetus (remaining organisms). In general maternal infections in very early pregnancy do not infect the placenta. Congenital infection in the first trimester is less common but generally more deleterious to the fetus than infection in the second trimester.

Pathology: Ascending fungal and bacterial infections cause chorioamnionitis (see below). Organisms limited to the intervillous space lead to accumulations of fibrin and predominantly chronic inflammatory cells at that location. The remaining infections lead to a diffuse chronic placentitis with chronic inflammatory cells in the chorion, decidua, and villous stroma(74). Unlike villitis of unknown etiology (see below), infectious villitis tends to involve most or all villi and to be associated with fibrosis, mineralization, remote villous hemorrhage, and sometimes plasma cells. Most infections also have unique features allowing a specific histopathologic diagnosis. These specific features include organisms or viral inclusions in the villous stroma (cytomegalovirus, herpes simplex virus, varicella zoster virus, Parvovirus B19, *T cruzi*), umbilical cord (*T pallidum*, *T gondii*), or intervillous space (*P falciparum*, *S hematobium*).

Clinical Correlation: A common clinical mnemonic for congenital infection is the acronym TORCH standing for toxoplasmosis, (others), rubella virus, cytomegalovirus, and herpes simplex(75). In the US two infections, CMV and syphilis account for more than 90% of congenital infections. Infants with any of the TORCH infections have a number of common features including IUGR, pancytopenia, hepatosplenomegaly, and coagulopathy. Each infection also has specific features, a description of which is beyond the scope of this chapter. A standard serologic screen known as the "TORCH titer" tests for maternal IgG specific for the common TORCH agents and is part of the routine workup for IUGR or suspected antenatal maternal infection. Specific testing for IgM testing is required to distinguish recent from remote infection. Many infections can also be diagnosed by PCR testing of fetal blood or amniotic blood obtained by amniocentesis.

2. Non-Infectious (Villitis of Unknown Etiology)

Background: Diffuse chronic villous inflammation with fibrosis and mineralization is typical of relatively rare TORCH-type congenital infections (see above). Localized lymphohistiocytic villous infiltrates are far more common being seen in approximately 5-10% of term pregnancies(76). While these localized infiltrates may reflect unrecognized infections, extensive investigation over many years has failed to reveal organisms and neither the mothers nor the infants of these pregnancies have shown any consistent clinical or laboratory evidence of an infectious process. Several investigators have shown that the villous infiltrates are largely composed of CD4-positive maternal T lymphocytes(77). It is currently believed that this lesion, known by convention as villous of unknown etiology (VUE), is the result of maternofetal cell trafficking with a localized host versus graft reaction in the villous tree. Maternofetal cell trafficking is a well-known phenomenon in animal and human pregnancies and can result in fetal graft versus host disease and later connective tissue disease(78, 79).

Pathology: The majority of cases of VUE consist of small groups of less than 5 affected villi in either a predominantly basal or random location. Less commonly, larger groups of villi are involved (patchy chronic villitis). When more than 5% of all villi are involved the term diffuse chronic villitis may be used. Stem villous vasculitis and perivasculitis is a special subcategory of VUE where lymphocytic spread is not confined to the terminal villi (obliterative fetal vasculopathy)(80). This pattern is often associated with extensive downstream avascular villi. All types of VUE are commonly accompanied by a lymphoplasmacytic infiltrate in the basal plate. Diffuse perivillous fibrin deposition and perivillitis with a polymorphous inflammatory infiltrate including neutrophils (active chronic villitis) are other variations usually seen with patchy or diffuse VUE. The presence of neutrophils, plasma cells, or eosinophils increases the possibilities of an underlying infectious etiology that can be further evaluated by special

AP103 Placental Pathology: Keeping It Simple and Focusing on What Matters

Raymond W. Redline, MD

stains and clinical correlation. Histiocytic giant cells, on the other hand, are common and do not suggest an infectious etiology.

Clinical Correlation: Focal and basal villitis are generally not associated with adverse outcomes(28). Basal villitis is more common with underlying uterine abnormalities such as malformations, leiomyomas, previous curettage, chronic endometritis, low implantation, and adherent placenta(81). Patchy and diffuse villitis are associated with IUGR, particularly when it occurs at term in the absence of hypertension(82). Stem villous vasculitis and perivasculitis with avascular villi is associated with an increased risk of cerebral palsy and other forms of neurologic impairment(27). Recurrent VUE in subsequent pregnancies occurs in 10-25% of cases(81, 83). This is particularly common with more severe involvement. A small subgroup of women experience recurrent fetal losses at all gestational ages secondary to diffuse chronic villitis.

Group 6: Fetal Vascular Obstructive Lesions

Background: Thromboocclusive lesions of large fetal vessels in the placenta and umbilical cord occur in the context of one or more of the classic triad of risk factors; vascular stasis, loss of surface resistance to coagulation, and circulatory hypercoagulability. Possible causes of fetal vascular stasis include prolonged umbilical cord obstruction, increased central venous pressure, and elevated hematocrit(84). Loss of surface resistance to coagulation may occur with severe fetal inflammation, antiphospholipid syndrome, and other forms of vessel wall damage. Circulatory hypercoagulability may be present with platelet disorders, maternal diabetes, or thrombophilic mutations involving protein C, protein S, antithrombin II, factor V, prothrombin 2010, and methyl tetrahydrofolate reductase. Other causes of inherited and acquired thrombophilia are emerging rapidly. It is likely that most cases of fetal thromboocclusive disease involve more than one risk factor.

Pathology: Sustained proximal vascular occlusion leads to degenerative changes in the distal villous tree. Because the tree branches extensively villous changes are a much more sensitive indicator of disease than the obstructive lesions themselves. Long-standing occlusion of large arteries leads to distal hyalinized avascular villi(85). The early stages of proximal venous occlusion cause circulatory stasis with degeneration of red blood cells, endothelial cells, and villous stromal fibroblasts (villous stromal-vascular karyorrhexis)(80). This pattern of change occurs diffusely in the placentas of stillbirths. When seen in a focal distribution in either live births or stillborns it has been termed hemorrhagic endovasculitis(86, 87). With long-standing venous obstruction, upstream villi become hyalinized and avascular as with arterial obstruction. These villous changes can affect large or small groups of villi and can be localized or widely distributed throughout the placental parenchyma. When the number of affected villi exceeds an average of ≥ 15 villi slide the process has been termed fetal thrombotic vasculopathy. Large vessel thrombi are identified in approximately one third of such cases. Other lesions associated with fetal thrombo-occlusive disease include intimal fibrin cushions and fibromuscular sclerosis of stem arteries(88). Intimal fibrin cushions are intramural aggregates of fibrin in proximal fetal veins that are usually attributed to increased intramural pressure. At late stages they may undergo mineralization. Fibromuscular sclerosis represents concentric narrowing of the vascular lumen by proliferating smooth muscle cells and subendothelial fibroblasts, typically occurring in placental vessels lying between the point of occlusion and the affected villi secondary to lack of flow.

Clinical Correlation: Fetal thrombotic vasculopathy is a significant risk factor for cerebral palsy and other forms of neurologic impairment in term infants(28, 89). It may also be associated with other manifestations of thromboembolic disease in the fetus including renal vein thrombosis, perinatal liver disease, and limb infarction(90, 91). Avascular villi are also associated with IUGR, chronic monitoring abnormalities, and discordant growth in twin gestations(82, 92). Nonocclusive thrombi in severely inflamed chorionic vessels are occasionally seen with severe acute chorioamnionitis in very low birth weight infants and represent a risk factor for neurologic impairment in this subgroup(93).

Group 7: Fetal Villous Capillary Lesions

Background: As described above early vascularization of the first trimester placenta occurs by vasculogenesis in which mesenchymal precursor cells form vessels under the inductive influence of

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**

Raymond W. Redline, MD

adjacent villous trophoblast. At later stages of pregnancy new vessels form by a process known as angiogenesis in which new vessels arise via budding and sprouting from existing vessels. Vascular endothelial growth factors such as VEGF and PlGF released under the influence of hypoxia, growth factors, or inflammatory cytokines can stimulate reactive villous capillary proliferations at several sites in the mature placenta(94). Isolated lesions in primary stem villi of the placenta are termed chorangiomas. Isolated or multifocal lesions affecting secondary or tertiary stem villi are termed chorangiomatosis and are most commonly seen in preterm placentas. Patchy or diffuse hypercapillarization of terminal villi is termed chorangiosis.

Pathology: Chorangiomas are spherical expansile lesions usually found under the chorionic plate or at the placental margins. Histologically they resemble capillary hemangiomas and are composed of a mixture of endothelial cells, pericytes, and myofibroblastic stromal cells. Associated nonspecific surface trophoblast proliferation is seen in up to 40% of cases and is benign(95). Chorangiomatosis generally arises in the loose reticular connective tissue of higher order stem villi. The lesion is composed of small vessels with endothelial cells and pericytes surrounding the central fibrovascular core. Rather than expanding eccentrically to form a mass as in chorangioma, the vessels in chorangiomatosis permeate diffusely up, down, and around the stem villus. Chorangiosis is generally confined to distal villi and vessels are lined by endothelium alone. The threshold for making a diagnosis of chorangiosis is the presence of 10 or more capillary cross sections in ten or more villi in several areas of the placenta(96). Generally occasional villi may be seen with 15-20 or more capillaries(97).

Clinical Correlation: Chorangiomas are increased in sites and scenarios associated with relative hypoxia such as the placental margin, preeclampsia, and multiple gestations(94, 98). They may be multifocal in rare cases and occasionally are associated with hemangiomas in the fetus. When large they can serve as niduses for fetal consumptive coagulopathy or may act as arteriovenous shunts leading to heart failure and hydrops fetalis(99, 100). Chorangiomatosis has similar associations with hypoxic sites and situations. It is also increased in Beckwith-Wiedemann syndrome and other cases with fetal congenital anomalies. Chorangiosis is most common in large diabetic placentas, but often accompanies placentas with other chronic and subacute pathologic processes(96, 101). It is also seen in placentas delivered at high altitude and may be a compensatory physiologic adaptation to the scenario of reduced oxygen tension without significant maternal perfusion of the intervillous space.

Group 8: Increased Fetal Nucleated Red Blood Cells

1. Fetomaternal Hemorrhage

Background: One of the consequences of the close proximity of maternal and fetal circulations in the placenta is that small tears in the villous tree can lead to fetal hemorrhage into the intervillous space. Some degree of fetomaternal hemorrhage has been estimated to occur in at least 50% of all pregnancies and fetal cells may persist in the mother for many years leading to modulation of the immune response and in some cases autoimmune diseases such as scleroderma(79). More substantial hemorrhages of 0.5-40 ml occur in 8% of pregnancies and hemorrhages of greater than 40 ml in 0.3-1% of pregnancies(102). Diagnosis of fetomaternal hemorrhages depends on the Kleihauer-Betke test, which is based on the enhanced ability of fetal hemoglobin to resist elution in an acid medium. The test is performed on a peripheral blood smear from the mother and the volume of fetal cells is from the percentage of acid resistant red blood cells and an estimate of the total maternal blood volume.

Pathology: Definitive diagnosis of massive fetomaternal hemorrhage can only be confirmed by direct measurement of fetal red blood cell in the maternal circulation. Placental findings which can suggest the diagnosis in the proper clinical context are markedly increased circulating fetal red blood cell precursors (see below), signs of developing placental hydrops (placentomegaly, villous immaturity, diffuse villous edema), and the finding of intervillous thrombi. Intervillous thrombi are spherical collections of clotted blood that are completely surrounded by villous tissue. They have been shown to represent sites of fetomaternal hemorrhage(103). However, they are extremely common and are not in most cases associated with large volume bleeds. The finding of multiple or large intervillous thrombi increases the probability of a clinically significant hemorrhage.

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**
Raymond W. Redline, MD

Clinical Correlation: Predisposing factors for massive fetomaternal hemorrhage include severe maternal underperfusion of the placenta, large edematous placentas associated with fetal congestive heart failure, and traumatic insults including abruptio placenta, amniocentesis, maternal trauma, or external cephalic version. Most cases have none of these predisposing factors(102). Cases may present in utero with decreased fetal movements, nonreactive fetal monitoring, or a distinct sinusoidal fetal heart rate pattern. Affected fetuses and neonates can develop circulatory collapse, CNS damage, hydrops fetalis, or stillbirth due to a combination of hypovolemia and chronic high output congestive heart failure due to profound fetal anemia(104).

2. Prolonged/Repetitive Antenatal Hypoxia

Background: Prolonged or repetitive shorter periods of antenatal fetal hypoxia are well-documented causes of central nervous damage in experimental pregnancy models and selected clinical cases(105). While in some cases the underlying cause of hypoxia is indicated by one or more of the pathologic lesions discussed above, in many cases the insults are not accompanied by recognizable tissue changes. One useful indicator of sustained significant hypoxia is the finding of an increased number of circulating NRBC in the placental circulation(106, 107). This physiologic response is the result of both premature release of red blood cell precursors into the systemic circulation and, later, increased fetal erythropoiesis. It is, at least in part, mediated by hypoxia-inducible elements in the promoter regions of erythropoietin.

Pathology: The identification of increased NRBC in the placental circulation is most important in cases such as stillbirths where early neonatal blood counts are not available. Clearly, direct enumeration of NRBC on peripheral smears is superior to their estimation in the placenta. Semiquantitative criteria for estimation of increased NRBC in the placenta have been described(28). Mild increase is 2-3 unequivocal normoblasts in one or more terminal villi in three or more 40x fields. Moderate increase is more than 3 normoblasts plus occasional more immature RBC precursors in one or more terminal villi in three or more 40x fields. Marked increase is mixed clusters of normoblasts and more immature RBC precursors in the majority of 40X fields. Cases with markedly increased NRBC are more likely the result of fetal anemia than hypoxia. Others have directly enumerated NRBC in the cross sections of large umbilical or chorionic vessels in the placenta(108).

Clinical Correlation: Increased NRBC can reflect problems in maternal oxygenation, delivery of oxygen to the fetal circulation, or insufficient oxygen carrying capacity in the fetus (anemia). Accumulation of red blood cell precursors in hematopoietic tissues and their subsequent release in large numbers in the fetal circulation requires a time interval measured in hours. Variable estimates of the time required vary from 2-24 hours and are controversial(109, 110). Variation may in part relate to the size of the NRBC pool in hematopoietic tissues that is available for acute release. While this is usually small it might be expanded by previous exposures to hypoxia. My own belief is that increased NRBC depend on both intensity and duration of hypoxia but that a marked elevation in a previously normal host probably requires 6-12 hours to develop. Persistence of elevated NRBC for several days postnatally suggests a longer period of antenatal hypoxia associated with markedly increased fetal erythropoiesis.

Group 9: Massive Perivillous Fibrin

Background: Massive perivillous fibrin deposition is characterized by the accumulation of excessive amounts of fibrin and extracellular matrix-rich fibrinoid around gas exchanging distal villi in the lower two thirds of the placenta(111-113). It should be distinguished from increased intervillous fibrin owing to maternal underperfusion and other causes of circulatory stasis usually begins around proximal villi in the upper portions of the placenta(42). Involvement of individual terminal villi in maternal underperfusion, nodular perivillous fibrin, is usually focal and related to villous repair(114). Deposition of fibrin and/or other matrix components provides a substrate that promotes differentiation of villous to intermediate trophoblast accompanied by migration into the intervillous space. The intermediate trophoblast also secretes additional fibronectin, which contributes to the accumulating fibrinoid matrix. The overall process recapitulates the normal formation of the basal plate and can be considered as a pathologic exaggeration of this process, which obliterates large portions of the distal villous tree. Massive perivillous fibrin deposition is idiopathic and often recurrent in subsequent pregnancies. While maternal

**AP103 Placental Pathology:
Keeping It Simple and Focusing on What Matters**

Raymond W. Redline, MD

underperfusion may play a role, it is unlikely to be the only factor involved. Maternal autoimmune disease, preeclampsia, and thrombophilic states have also been implicated(115-117). Case reports of discordancy in twins and an association with fetal LCHAD disease suggest a fetal genetic component as well(118, 119).

Pathology: Massive perivillous fibrin deposition occurs in two distinct patterns; basal-predominant with a rind-like gross thickening of the basal plate and diffuse with fine lacy strands of firm with fibrin marbling the entire cut surface of the placenta. Microscopically, distal villi are surrounded by a matrix of fibrin and fibrinoid elements intermixed with large numbers of intermediate trophoblast (so-called X-cells). In some cases degenerative changes such as eosinophilia or karyorrhexis of villous trophoblast and stroma may be seen. The lesion is distinguished from villous infarction by failure of the villi to agglutinate with one another and the absence of degenerating debris in the intervillous space. Localized plaques of perivillous fibrin are common in term placentas and increased intervillous fibrin in areas of marginal placental atrophy is common at all gestational ages(120). These localized lesions should not be mistaken for massive perivillous fibrin deposition.

Clinical Correlation: Massive perivillous fibrin deposition (“maternal floor infarction”) is a rare but extremely serious lesion associated with spontaneous abortion, stillbirth, severe IUGR, and neurologic impairment(112, 113) (121). It is an important cause of recurrent reproductive failure(122). It most commonly begins in the late second and early third trimester and can develop quite rapidly. It has been associated with a typical sonographic picture which some have termed a “jelly-like” placenta(123). Severe IUGR, decreased pulsed flow doppler studies, and abnormal biophysical profile are common and delivery at the earliest possible opportunity is recommended(124). No controlled trials of therapy have been conducted. Empiric use of heparin, aspirin, or immunomodulatory agents has been attempted in some cases.

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Raymond W. Redline, MD

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Raymond W. Redline, MD

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