PLACENTAL PATHOLOGY

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This set of lectures is designed to review the gross and histologic criteria used in the diagnosis of common placental pathology. I have included some clinical correlation but have not discussed pathogenesis in detail. At the end of these notes are templates we use at Northwestern University for signing out placentas. I would like to acknowledge Dr. Linda Ernst (Head of the Perinatal Service at Northwestern) for her outstanding knowledge, collegiality and organizational skills and who established the high-quality perinatal service at NU before I arrived. In addition, I am indebted to Dr. Don Singer, who mentored me through innumerable difficult perinatal and placental cases while I was an Assistant Professor at the University of Wisconsin-Madison.

NORMAL HISTOLOGY REVIEW:

1) Membranes: The amnion lines the amniotic sac containing the fetus. The amnion consists of a single layer of cuboidal epithelium, its basement membrane, and a collagen layer. The chorion lies deep to the amnion and consists of a sparsely cellular collagen layer. The chorion rests on a layer of intermediate trophoblast cells (clear to eosinophilic cytoplasm). Amnion, chorion, and intermediate trophoblast cells are fetal in origin. Deep to the intermediate trophoblast layer is the decidual layer (maternal in origin). This layer contains decidualized maternal cells, vessels, fibrin, and often some degree of hemorrhage.

2) Umbilical cord: The outer surface of the umbilical cord is covered by a single layer of cuboidal amniotic epithelium. There is often focal squamous metaplasia. Normally, 3 vessels (2 arteries and 1 vein) are embedded in a myxoid paucicellular matrix (Wharton's jelly).

3) Placental disk: The chorionic plate (fetal surface) consists of a single layer of cuboidal amniotic epithelium overlying a paucicellular collagenous matrix (chorion) containing numerous large vessels of fetal origin. Below this are the fetal villi (large stem villi to small terminal villi) separated by clear or blood containing spaces (the intervillous space) where the maternal blood circulates around the fetal villi. The sizes of the villi vary depending on the gestational age. The villi consist of an outer layer of syncytial trophoblast cells in immediate contact with the maternal blood in the intervillous space. Immediately deep to the syncytial trophoblast cells is a single, discontinuous layer of cytotrophoblast cells (larger, cuboidal cells). As gestation proceeds these become more difficult to identify. The cellular matrix consists of macrophages (Hofbauer cells) and fibroblasts with numerous vessels (capillaries in the terminal villi and larger muscular vessels in stem villi). As maturation proceeds the capillaries in the terminal villi appear to move closer to the syncytiotrophoblast layer, which
increases diffusion efficiency. In addition, the terminal villi get smaller and more numerous, and syncytial knots (Tenny-Parker change) increase. Calcifications also increase as term approaches.

The basal plate (maternal surface) consists of intermediate trophoblast cells, decidualized maternal cells, at least two well defined fibrinoid layers (Rohr's (adjacent to intervillous space) and Nitabuch's (a deeper layer that separates intermediate trophoblast cells from decidua), and maternal vessels. The maternal vessels here should be assessed for fibrinoid necrosis and atherosclerosis. Normally, these vessels are invaded by trophoblast to open them up and widen their lumens leading into the sinusoidal intervillous spaces. The invading trophoblast can resemble macrophages and fibrin-like changes can occur around these vessels mimicking fibrinoid necrosis.
Term Villi

Basal Plate

Nitabuch’s fibrin
Decidua
Rohr’s fibrin
Intermediate Trophoblast
Villi
PATHOLOGY OF THE PLACENTA:

I. GROSS PATHOLOGY

A. Size and shape: The size and shape of the placenta is critical and is the lead off line in our surgical pathology reports. The weight of the placenta and the three dimensions of it's size are recorded in the gross description. The measured weight is compared to standard tables (Pinar H et al. Reference values for singleton and twin placental weights. Pediatr Pathol Lab Med 16:903, 1996) and reported as large, small or appropriate for gestational age depending on whether the weight is greater than the 10%, less than the 10% or within the expected range.

1. Shape: A normal placenta is round to ovoid although multiple irregular shapes are possible as a result of disease (large remote infarct), manner or site of implantation, or atrophy. Dumbbell shaped placentas can occur where there is still parenchyma attaching both lobes. Abnormally shaped placentas probably arise due to abnormalities in the decidualization or vascularization of the uterus resulting in local atrophy and irregular growth (e.g. implantation over a leiomyoma).

In multilobed placentas there is true separation of the lobes by a segment of intervening membranes. A bilobed placenta has two lobes of approximately equal size (2-8% of placentas). If one lobe is smaller than the other then it is reported as an accessory or succenturiate lobe (5%). Umbilical cord insertion can be into either lobe (usually the dominant lobe) or velamentous. Membranous vessels are always present by definition. These vessels should be inspected carefully for possible thrombi, compression or rupture. Multilobed placentas are associated with vaginal bleeding, postpartum hemorrhage, placenta previa and retained placenta. The pathogenesis leading to each of these associations is not necessarily well understood.

2. Size: Large for gestational age placentas (>10 percentile) can occur in a number of clinical circumstances including diabetes, hydrops (from any cause), genetic background (normal variation), mesenchymal dysplasia, infections (classically syphilis), maternal obesity, unknown, others.

Small for gestational age placentas (<10 percentile) can occur as a result of maternal vascular underperfusion related to chronic hypertension or preeclampsia, from multiple infarcts, as a result of massive perivillous fibrin deposition, underlying maternal diseases (heart and kidney), associated with chronic villitis (either infectious or villitis of unknown etiology), in severe fetal thrombotic vasculopathy with extensive avascular villi, due to genetic background (normal variation including ethnicity), and frequently for unknown reasons.

Appropriate for gestational age placentas can still demonstrate severe pathology.
B. Membranes & chorionic plate: Normal membranes are clear and colorless. Acute chorioamnionitis can result in opaque membranes due to the presence of inflammation. The passage of meconium can also cause opacification and discoloration (brown to green). Chronic or large remote marginal of fetal plate hemorrhages can result in the accumulation of numerous hemosiderin laden macrophages in the membranes or at the chorionic plate and give a brown to tan discoloration to the membranes.

Normal membranes insert at the margin of the placenta. When the membranes insert closer to the central portion of the placenta than at the margin this is referred to as circummarginate insertion (reported in up to 25% of placentas). If there is folding of the membranes to form a ridge at the site of insertion this is referred to as circumvallate insertion (occurring in 1-5% of placentas). Both are referred to as extrachorialis membrane insertion and this is relatively easy to assess by simply holding the membranes above the surface of the placenta and determining whether a portion of placental tissue protrudes past the insertion rim. We report the percentage of the circumference that is circummarginate (rarely complete) and the greatest amount of protruding placenta as X cm of extrachorialis placenta. Histology at the site of membrane insertion in these cases often reveals hemosiderin and increased fibrin. The pathogenesis leading to extrachorial placentation remains controversial, but a widely accepted model is that marginal hemorrhage undermines the membrane insertion site. Circummarginate and circumvallate membrane insertion seem to represent the same process but traditionally circummarginate insertion is not associated with adverse outcomes, whereas circumvallate insertion is associated with an increased risk of antenatal bleeding and premature delivery. Both can be associated with marginal hemorrhages, but the clinical significance of these hemorrhages is unknown.

We also indicate in our gross description the site of membrane rupture relative to the margin if it can be determined. Membrane sections should be taken to include the insertion site.

Other membrane and chorionic plate findings include various cysts (amnionic epithelial inclusion cysts, subchorionic cysts and pseudocysts), yolk sac remnants, vernix caseosa (small collections of squamous cells and hair derived from the amnion), and amnion nodosum (often associated with prolonged oligohydramnios). Subamnionic hemorrhages are common and usually occur intra- or post-partum. Subchorionic hemorrhages or fibrin thrombi are very common occurring in up to 60% of placentas. These usually occur as white plaques visible at the chorionic plate surface. Microscopically they are laminated fibrin thrombi and often contain hemosiderin. Subchorionic fibrin thrombi have been associated with preterm birth, abortion, vaginal bleeding, intrauterine growth restriction (IUGR), and fetal demise, however, most are associated with a normal pregnancy. They are more commonly found in placentas of mother’s with severe heart disease or thrombophilias. A more extensive form of subchorionic
hemorrhage is referred to as the Breus mole. The etiology leading to this large bosselated subchorionic hemorrhage is unknown.

C. **Basal plate & parenchyma:**

1. Hemorrhages (including abruption): **Background:** A variety of hemorrhages can be identified grossly and are often described by their location. These include marginal or retroplacental hemorrhages (can be associated with abruption or occur peripartum), intervillous thrombi (usually pale laminated lesions that can occur anywhere in the placenta), and acute parenchymal hemorrhages (usually dark red and laminated but with more red blood cells). All retroplacental hemorrhages are not abruptions. A retroplacental hemorrhage is defined as hemorrhage at the site of placental separation from the uterus and may occur antepartum (these may be clinically silent or significant), peripartum, or following the delivery of the infant and as part of normal delivery of the placenta. Abruption is defined as a clinically significant antenatal detachment of the placenta usually with associated retroplacental hemorrhage. The result can be severe fetal hypoxic injury or death. Multiple causes for acute abruption include maternal vascular disease (hypertension, preeclampsia, thrombophilias, and autoimmune diseases), trauma, amniocentesis, uterine anomalies, placenta previa, folic acid deficiency, substance abuse including cocaine and nicotine, and multiparity. The most common causes being maternal vascular diseases and trauma from MVA. The frequency of abruption is estimated at about 1-4% of all deliveries. The placental separation can be complete (rare) or partial. The clinical triad includes vaginal bleeding, pain, and rigid abdomen. Acute abruption is usually thought to involve disruption of maternal arteries. **Pathology:** Acute retroplacental hemorrhages that occur less than an hour before delivery cannot be distinguished from normal postpartum blood clot. It takes several hours for an antenatal retroplacental hemorrhage to become firmly attached to the placenta grossly. The underlying placental parenchyma becomes compressed and with extended time will infarct. The RBCs breakdown with hemosiderin accumulation (4-5 days) and increased perivillous fibrin deposition. Other findings suggestive of maternal vascular underperfusion should be sought. If the hemorrhage is large and has been present for an extended time it will indent the maternal surface. The correlation between pathologic and clinical abruption is poor. I rarely will call retroplacental hemorrhage an “abruption” straight out in the diagnostic line. If there is a good clinical history of suspected abruption and I find gross and histologic evidence of a retroplacental hemorrhage I will usually call it a “acute/subacute/remote retroplacental hemorrhage (measuring XXXcm in greatest dimension) consistent with the clinical history of possible abruption.”

**Clinical associations:** Acute abruption is associated with numerous adverse outcomes including preterm delivery, IUGR, stillbirth, and hypoxic/ischemic brain injury. Chronic abruption is thought to involve venous disruption rather than arterial. Chronic abruption is associated with multiparity, smoking, oligohydramnios and deep uterine implantation. Chronic abruption is associated with other placental findings including remote marginal hemorrhage with hemosiderin, membranes or chorionic plate with hemosiderin laden
macrophages, and circumvallate membrane insertion. Chronic abruption is associated with an increased risk of preterm delivery, cerebral palsy and other neurologic impairment in term infants.

2. **Intervillous thrombi:** **Background:** Intervillous thrombi are common, occurring in up to 20% of term placentas. The origin of the blood has been found to be fetal in many cases. There is an association between fetomaternal hemorrhage and the presence of intervillous thrombi. The diagnosis of fetomaternal hemorrhage must be made by flow cytometry or a Kleihauer-Betke test on maternal blood as there are no specific gross or histologic findings that are diagnostic. Intervillous thrombi can also result from thrombosis of maternal blood in the intervillous space. Maternal disease states such as thrombophilias or preeclampsia (diminished perfusion) are associated with increased likelihood of intervillous thrombi. **Pathology:** Grossly these thrombi can be red if acute or pale tan to white if remote and are usually well demarcated parenchymal lesions. As they age the laminations become evident and these lesions can usually be accurately diagnosed grossly. Histology reveals expansion of the intervillous space by layers of fibrin and red blood cells. Villi do not routinely become "entrapped." If large, the adjacent villi can become infarcted and show evidence of ischemic change (distal villous hypoplasia and increased syncytial knots). These lesions should be sampled, examined histologically and reported.

3. **Villous infarcts:** **Background:** Placental infarcts represent localized areas of ischemic necrosis of villi usually due to diminished maternal perfusion to the intervillous space. Small infarcts are common and can be seen in up to 25% of normal pregnancies and are commonly seen at the margin. They are found much more commonly in placentas from patients with hypertension or preeclampsia. **Pathology:** Grossly acute infarcts tend to be red and change to white with time. They usually have well defined borders and lack the laminations seen in intervillous thrombi. Microscopically the earliest change is loss of the intervillous space with villous crowding. There is usually increased perivillous fibrin deposition in some of the remaining intervillous spaces and around the outside of the ischemic area. Acutely there can be a brisk acute inflammatory response to the infarcted necrotic tissue. With time the nuclear chromatin within cells of the affected villi clumps and eventually fades away leaving pink acellular villi (ghost villi) with increased surrounding fibrin. Remote infarcts can have increased calcification. The surrounding villi that survive often show evidence of hypermaturation (distal villous hypoplasia and increased syncytial knots). Organization and fibrotic scarring as occurs in myocardial and other organ infarcts do not occur in placental infarcts. **Clinical associations:** It has been estimated that over 50% of the parenchyma must be infarcted to result in fetal demise, but I believe it is much more complicated than that and that any given percentage of infarction cannot directly predict the likelihood of fetal death. Clinically infarcts are associated with maternal vascular underperfusion due to the disease states listed below. There is a strong correlation between the presence and amount of infarcted placenta and IUGR and a small placenta.
4. Chorangioma: **Background:** Chorangioma represents a discrete neoplasm of benign proliferating capillaries and stroma occurring within a villous and can be identified grossly as a bulging red to white mass. This is different from chorangiosis and chorangiomatosis which are not identifiable grossly (see later). **Pathology:** Histologically chorangiomas are composed of proliferating fetal blood vessels and a variable amount of fibrous and cellular stroma. **Clinical associations:** These are rare lesions but are seen more commonly in multiple gestations and neonates with congenital anomalies. The clinical consequences include fetal hydrops, stillbirth, IUGR, fetal anemia and thrombocytopenia, fetal congestive heart failure, DIC, premature delivery, abruption, and preeclampsia.

5. Calcifications: Calcifications of the basal plate and parenchyma are more likely with increased gestational age and are commonly prominent in late and post-term placentas. Calcifications can occur with or without other placental pathology. In general I will comment on the presence of increased calcifications in a report only if there is extensive calcification in almost all fields on most slides. The clinical significance, if any, is not usually clear.

6. Intervillous fibrin: Increased basal plate and/or intervillous fibrin raises concern for possible massive perivillous fibrin deposition/maternal floor infarct (see below). Grossly visible intervillous fibrin appears as white to tan curvilinear strands running through the parenchyma. Increased basal plate fibrin appears as a rind of white firm material 1-3mm thick covering all or part of the maternal surface, and is best appreciated on cut section. Estimated pathologic amounts of intervillous fibrin range from 30-50% of the total intervillous space.

D. **Umbilical cord:**

1. Embryonic remnants: Different types of remnants that can be found in the umbilical cord include allantoic duct remnants (usually found between the 2 umbilical arteries), omphalomesenteric duct remnants (usually at periphery of cord), and vitelline vessels. We do not report these.

2. Umbilical cord insertion: Most commonly the umbilical cord inserts centrally or eccentrically (>90%). These insertions are not associated with pathology. Marginal insertion (< 1cm from the true disc margin) occurs in about 7% of placentas. The clinical significance remains debated, but marginal insertions have been reported to be associated with preterm labor, neonatal asphyxia, abortions and malformed infants. We do report these in the diagnostic line of our report. Velamentous cord insertion is when the cord inserts into the membranes rather than into the disc and occurs in about 1% of singleton placentas, but with a much higher likelihood in twins. The pathogenesis remains unknown. Velamentous cord insertion has important clinical consequences. The vessels within the membranes are prone to trauma, rupture, compression and thrombosis and velamentous cords can result in the histologic changes associated with fetal vascular obstruction (see later). The velamentous vessels can also present during delivery prior to the fetus (vasa previa) with adverse consequences including rupture of the vessel(s) with massive fetal hemorrhage.
Velamentous cords are associated with low birth weight, low Apgar score, abnormal fetal heart rate patterns, prematurity, cerebral palsy, death, early abortion, and congenital anomalies. We always report velamentous insertion in the diagnostic line. Furcate cord insertion is rare and is defined by the umbilical vessels splitting and leaving Wharton’s jelly prior to reaching the chorionic plate surface. Most infants with furcated cord insertion are normal, however, there is a weak association with stillbirth, thrombosis of fetal vessels, IUGR, and hemorrhage. Velamentous and furcated cord insertion can be difficult to distinguish from each other grossly in some cases.

3. Coiling: There are numerous papers written on umbilical cord coiling or “twist.” We determine the coiling index (number of twists (coils) per 10 cm of cord) for all placentas. A normal coiling index is between 1 to 3 coils per 10 cm of cord. Less than 1 coil per 10 cm is considered undercoiled (hypocoiled) and >3 coils/10 cm is considered hypercoiled (10-20% of placentas). Coiling of the umbilical cord is thought to be a result of fetal movement. Focal areas of hypercoiling and localized strictures can be identified. The significance of umbilical cord strictures in cases of prolonged intrauterine fetal demise remains controversial. Additional pathologic evidence of mechanical obstruction to fetal blood flow should be sought to invoke an umbilical cord stricture as the cause of IUFD. Both hypocoiling and hypercoiling are associated with an increased risk of IUGR, fetal distress, and perinatal death. We always report abnormal coiling in the diagnostic line of our reports.

4. Length and diameter: Normal umbilical cord length at term is 60 +/- 13 cm. Cord length increases with gestational age and appropriate tables should be consulted for gestational age (Naeye RL. Umbilical cord length: clinical significance. J Pediatr 107:278, 1985). In addition, genetic factors and fetal movement have been proposed to determine the length of the umbilical cord. Excessively long cords occur in about 5% of placentas and short cords occur in about 1-2% of placentas. Care must be taken in reporting a short cord as seldom is the entire cord submitted to pathology for evaluation. Long UCs are associated with cord accidents and entanglements (including nuchal cord), cord prolapse, true knots, excessive coiling, constrictures, and thrombi. The clinical consequences of excessively long cords have been studied and include fetal distress, neurologic impairment, IUGR, and IUFD. Abnormally short cords are associated with cord hemorrhage, abruption, failure of descent, prolonged second stage of labor, fetal distress, low Apgar scores and fetal developmental and congenital anomalies (abdominal wall defects and amniotic band disruption sequence). We always report an abnormally long cord length in the diagnostic line of our reports. The expected cord diameter at term is between 1.2 and 1.7 cm but there can be segmental variation. Significantly increased cord diameters are often secondary to edema. An edematous cord by itself is not associated with an increased risk of an adverse outcome. Abnormally thin cords are associated with IUGR. There is a potential risk that the diminished Wharton’s jelly can predispose the vessels to injury and rupture. Thin cords can occur in
the setting of oligohydramnios from a variety of causes including maternal vascular underperfusion.

5. Umbilical cord hemorrhage: Cord hemorrhages can be seen grossly and/or histologically. If acute, which most are, one must be careful in ascribing significance to the hemorrhage. Most are likely the result of cord traction during removal of the placenta and occur following delivery of the infant. There are cases where a cord hemorrhage may be significant, such as intrauterine fetal demise, and additional supporting pathologic evidence of a clinically significant UC hemorrhage must be sought.

6. Umbilical cord vessel number: The normal constellation of umbilical blood vessels is 2 arteries and 1 vein. In less than 1% of singleton pregnancies and in up to 9% of twin pregnancies there may be a single umbilical artery (SUA) or two vessel umbilical cord. Occasionally a small remnant of the other artery can be identified. The umbilical arteries can fuse away from the insertion site so one section may have three vessels and another only two. This fusion is called Hyrtl’s anastomosis. Although most infants with a single umbilical artery have a normal outcome there is an associated increased risk for IUGR, antepartum hemorrhage, polyhydramnios and oligohydramnios. Mothers with diabetes are more likely to have infants with SUA than nondiabetics. In autopsy studies fetuses with a SUA have a high likelihood of other congenital anomalies, especially involving the kidneys. Interestingly, it is usually (about 75%) the left umbilical artery that is absent. The etiology is not well understood but in many cases it is thought to represent atrophy of one artery due to a diminished downstream area of villous perfusion. Accessory blood vessels in the umbilical cord are rare and can represent an aberrant right umbilical vein or more likely persistence of one or more vitelline vessel.

7. Knots: True umbilical cord knots are rare (<1%) and are classified as tight (clinically relevant) and loose (probably not important). Tight knots can result in umbilical vein compression with stasis and congestion of the vein. If long standing an umbilical vein thrombus can develop. Sections should be taken from both sides of a knot to look for congestion and thrombosis. False knots are due to redundancy in fetal vessels in the cord and have no clinical significance. Tight knots are often seen in association with long cords, monoamnionic twinning, and multigravidas. Clinically tight knots increase the risk for intrauterine and intrapartum demise (up to 10% mortality) and the risk for a poor neurologic outcome. We report all true knots in the diagnostic line as either tight or loose.

8. Thrombi: Background: Umbilical cord thrombi occur in about 1:1300 deliveries. Umbilical cord vein thrombosis is more common, whereas arterial thrombosis is more likely to result in fetal death. Pathology: Thrombi within the umbilical cord can result in focal areas of vascular swelling and/or discoloration. These areas should be examined closely and if a thrombus is suspected, histologically examined. Microscopic features of a true thrombus need to be identified including dilation of the caliber of the involved vessel, a fibrin thrombus (multiple layers of fibrin and blood) within the lumen, attachment to the wall of the
vessel, and/or organization. Depending upon how acute the thrombus may be, identification as a true thrombus can be difficult. Fibrin thrombi do not occur post-mortem. **Clinical associations:** Umbilical cord vascular thrombi are associated with cord abnormalities (velamentous insertion, true knot, inflammation, entanglement (nuchal or shoulder), hypercoiling, amnionic bands, diabetes, thrombophilias (controversial) and others). The clinical consequences of umbilical cord thrombosis can be grave including death, IUGR, and neurologic injury including neonatal stroke and/or thrombosis possibly from embolic events.

**Additional references:**


II. AMNIONIC FLUID INFECTION (AMNIONIC INFECTION SYNDROME)

**Background:** Infections during pregnancy that affect the placenta can occur via 2 main routes: ascending (usually bacterial) infections from the vagina/cervix and hematogenous spread from the maternal circulation (more commonly viral and parasitic – TORCH, but bacterial infections can also occur – Listeria). Less commonly, infections involving the placenta and/or fetus can be acquired by direct inoculation from a diagnostic procedure such as amniocentesis or chorionic villous sampling or from direct extension of infections from adjacent organs including the endometrium (maternal chronic deciduitis). This section focuses on the pathologic findings associated with an ascending bacterial infection resulting in amnionic fluid infection that is often referred to as acute chorioamnionitis. The presence of the infectious agent induces an acute inflammatory response, usually first inciting maternal neutrophils and later fetal neutrophils. Early studies implicated the extent and severity of the inflammation in being associated with poor fetal outcomes such as preterm premature rupture of membranes, anoxic injury including cerebral palsy, thrombosis, and fetal sepsis. In an effort to better classify the inflammation associated with ascending bacterial infections a systematic pathologic classification scheme was developed about 10 years ago (Redline RW et al. Amniotic infection syndrome: Nosology and reproducibility of placental reaction patterns. Pedatr Devel Pathol 6:435-448, 2003). At Northwestern we use a slightly modified version of this scheme for reporting acute amnionic fluid infection.

**Pathology:** Acute chorioamnionitis can be divided into two components, the maternal inflammatory response and the fetal inflammatory response. Each of these is then assigned a stage (based on the location and extent of inflammation) and grade (based on severity). We primarily report stage. The stage of the maternal inflammatory response in the membranes and chorionic plate are referred to as 1) acute marginating choriodeciduitis (sub-chorionitis) if the neutrophils are restricted to the subchorionic fibrin and decidual-chorionic interface; 2) acute chorioamnionitis if the neutrophils have entered the chorion and/or amnion; and 3) necrotizing chorioamnionitis if there is clear evidence of amnion necrosis (not just separation of the amnion from the chorion). The grading is based on the number of neutrophils within a cluster with less than 10-20 neutrophils per cluster being grade 1 and anything more than 10-20 being grade 2. We do not routinely grade the maternal inflammatory response. The stage of the fetal inflammatory response in the umbilical cord and chorionic plate vessels are referred to as 1) chorionic plate vasculitis or umbilical cord phlebitis (only the vein is involved); 2) if one or more of the umbilical arteries is involved the inflammation is a stage 2 and referred to as umbilical arteritis. If all vessels of the umbilical cord are involved this is still stage 2 but we refer to this as panvasculitis; 3) acute inflammation encircling the vessels with associated vessel wall or Wharton’s jelly necrosis is stage 3 (this is relatively rare). Grading of the fetal inflammation involves the extent of the inflammation and the presence of confluent collections of neutrophils (grade 2) and if less than this, it is assigned stage 1. By this definition a stage 3 fetal inflammatory response is also a grade
2. Again we primarily report the fetal inflammatory response stage. We always comment on the presence of associated intravascular thrombi as this has been reported to be associated with an increased risk for neurologic impairment. If the acute inflammation extends out into Wharton’s jelly but does not reach stage 3 levels we refer to the vessels involved and state there is also “funisitis.”

Peripheral funisitis: Candida infections frequently result in microabscesses at the outer periphery of the umbilical cord +/- fetal vasculitis, so we always survey the entire cord under the microscope at low power. If peripheral microabscesses are seen we always perform a PAS or GMS stain. If there are only peripheral microabscesses and no vasculitis we use the terminology “peripheral funisitis with microabscesses”. If yeast/fungus is identified within the umbilical cord (candida funisitis) of a live neonate we consider this a “critical value” and call the clinician. While the risk of the neonate becoming ill is relatively low (<10%) those that do show signs of sepsis within the first week of life are at increased risk for poor outcomes because they are usually treated as bacterial infections and not as yeast sepsis.

Subacute chorioamnionitis represents mixed acute and chronic inflammation involving the chorionic plate and/or membranes and is thought to represent a more chronic infection perhaps by an organism with low pathogenicity.

Acute villitis and intervillositis represents acute inflammation (neutrophils) involving the villi and adjacent intervillous space, usually with direct injury to the involved villous. There may be microabscesses. This should raise suspicion for Listeria monocytogenes infection. However, other organisms (E. coli, group B streptococcus (GBS), and others) can less commonly result in a similar pattern. In addition, acute villitis or acute intervillositis can be seen in severe maternal septicemia.

Clinical associations: Acute chorioamnionitis with the associated fetal vasculitis represents the maternal and fetal reactions, respectively, to an ascending maternal bacterial infection. Chorioamnionitis in a preterm pregnancy can result in preterm premature rupture of membranes and/or premature labor. It is estimated that 50-60% of all preterm placentas have evidence of amnionic fluid infection. In most cases there is a general consensus that the infection precedes and probably causes the rupture of membranes. However, prolonged rupture of membranes for any reason (prior infection, incompetent cervix, hemorrhage, others) predisposes the mother to a secondary ascending infection. Bacterial vaginosis is a known risk factor for infection as well. These premature neonates often develop complications associated with prematurity including possible fetal/neonatal sepsis. In near-term and term fetuses, chorioamnionitis does not lead to fetal death unless there is also evidence of fetal pneumonia, sepsis or thromboemboli. Chorioamnionitis at or near term is common and is usually an incidental finding (20% of deliveries). The presence of a fetal inflammatory response, especially if one or more arteries are involved by inflammation, indicates a higher likelihood of fetal exposure to the inciting agent and possible fetal complications. In addition, studies have indicated that the amount of the
fetal inflammation (grade) is associated with higher likelihood of cerebral palsy and poor neurologic outcomes. The older term for the fetal inflammatory response was funisitis, but should now be referred to as fetal vasculitis if 2 or more vessels are involved or phlebitis (vein) or arteritis (artery) if a single vessel is involved. The term funisitis is now used to refer to neutrophils in Wharton’s jelly. While there is little doubt that the specific causative organism leading to the ascending infection is important for neonatologists in order to treat suspected neonatal sepsis, identification of the causative organism from the placental tissue is difficult for the pathologist. Gram stains can be helpful in selected cases (GBS, fusobacteria, or listeria), but placentas are frequently contaminated by vaginal and fecal flora so interpretation of a causative organism should be made with care. We do not routinely culture placentas and rarely perform gram stains.

Additional references:


III. CHRONIC VILLITIS

Background: Chronic villitis is defined as chronic inflammation (lymphohistiocytic with or without plasma cells) involving the chorionic villi. Chronic villitis can be separated into 2 broad categories based upon etiology, although the histologic findings seldom distinguish between them. Chronic villitis can be due to infectious agents or villitis of unknown etiology (VUE). Chronic villitis from the combined causes is relatively common, being found in about 10-
15% of all placentas. Infectious causes for chronic villitis are due to the hematogenously spread transplacental agents which include the TORCH infections. Common infectious agents leading to chronic villitis include CMV and syphilis and others less commonly include Toxoplasma gondii, rubella, herpes, varicella zoster, hepatitis B and C, poxviruses, enteroviruses, parvovirus B19, HIV, spirochetes, parasites, and others. Chronic intervillositis without villitis is more commonly seen due to P falciparum (malaria) and B burgdorfei (lyme disease). The details of each of these infectious agents and the associated placental pathology are well described in Manual of Pathology of the Human Placenta 2nd ed. RN Baergen Springer Science 2011. In general, infectious causes for chronic villitis are reported to represent only 5% of all chronic villitis cases, however, our experience is that it may be even less. The inflammatory infiltrate in infectious causes and non-infectious causes are similar, although it is reported that the presence of plasma cells, fibrosis, and mineralization of the involved villi should raise greater concern for infectious etiologies. Our practice is to look carefully for viral inclusions by H&E (CMV, parvovirus, herpes) or toxoplasmosis cysts and order a CMV immunohistochemical stain if the amount of inflammation is severe (see below) or we are concerned based on the H&E findings. If the inflammation is predominantly granulomatous (this could still be VUE) or there are necrotizing granulomas we will order stains for acid fast bacteria (concern is for TB or leprosy – both very rare). Villitis of unknown etiology (VUE) which accounts for more than 95% of chronic villitis is essentially defined by the lack of a clear cause. It is now thought that most of these cases represent alloimmune mediated villous injury. The majority of the lymphocytes and histocytes involved in the villous destruction have been shown to be of maternal origin and it is thought that there is a maternal inflammatory response (CD3 positive maternal T-cells) to some unknown fetal antigen (a graft-versus-host like reaction). This would explain the high recurrence rate.

**Pathology:** Chronic villitis due to VUE usually shows nonuniform (multifocal) involvement of the placenta. The chronic inflammatory infiltrate of lymphocytes, histocytes (including histiocytic giant cells) and plasma cells has been classified into low and high grade villitis based upon the number of involved villi (see Redline RW Villitis of unknown etiology: noninfectious chronic villitis in the placenta Hum Pathol 381439-1446, 2007). Less than 10 villi per cluster involved by inflammation is classified as low grade and if there are more than 10 villi per focus this is classified as high grade. Each of these is then further staged based upon the extent of placental involvement. Low grade chronic villitis can be focal (only one slide involved) or multifocal (more than one slide involved). High grade villitis can be staged as diffuse if >5% of all placental villi are involved by inflammation and called patchy if <5% are involved. There are multiple patterns of involvement of the placenta by chronic villitis (see above paper for details). The inflammation is thought to result in fetal vascular destruction in terminal villi and can result in avascular villi which is a common associated finding. The presence of avascular villi should raise concern for one of two entities (chronic villitis or fetal vascular obstruction (fetal thrombotic vasculopathy)) and prompt a search for additional evidence for these. In severe forms of chronic villitis...
obliterative fetal vasculopathy can be seen. These areas show villous vascular wall injury and these vessels may contain thrombi. Concern should be raised for possible syphilis which results in a villous endarteritis that can appear similar, but usually has more plasma cells. Chronic villitis is often associated with placental findings including chronic deciduitis with plasma cells, chronic chorionitis, increased perivillous fibrin, occasionally chronic intervillositis, and more recently eosinophilic/T-cell vasculitis.

**Clinical association:** Diffuse high grade chronic villitis is associated with a high recurrence rate (10-25%) and poor outcomes including IUGR, premature delivery, adverse neurologic outcomes, and stillbirth. Low grade or basal chronic villitis are usually not associated with adverse outcomes. Basal villitis is defined by the restriction of the chronic inflammation to villi near the basal plate. Basal villitis can be seen in association with leiomyomas, uterine malformations, chronic endometritis and abnormal placental implantation (retained placenta, placenta accreta). A poorly understood association exists between fetal alloimmune thrombocytopenia and VUE (Althaus J 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; 193:1100-1104). We have seen 2 cases of neonatal alloimmune thrombocytopenia with severe diffuse chronic villitis in the last year and it is important for the neonatologists to recognize this association to provide proper treatment for the thrombocytopenia.

**Additional references:**


IV. MATERNAL VASCULAR UNDERPERFUSION

**Background:** Maternal vascular underperfusion of the intervillous space (also known as uteroplacental insufficiency or placental malperfusion) occurs from a variety of causes. Systemic maternal diseases such as severe heart disease, diabetes mellitus, maternal hypertension (chronic or pregnancy induced hypertension and preeclampsia/eclampsia), thrombophilias (factor V Leiden mutation, deficiency of antithrombin III, protein C or S deficiency, hyperhomocysteinemia, prothrombin mutation), autoimmune disorders (particularly systemic lupus erythematosus), antiphospholipid antibody syndrome, chronic renal failure, and abnormalities of the maternal arteries supplying the uterus can result in diminished blood flow to the uteroplacental vascular bed. Despite years of research the exact pathophysiologic events mediating diminished placental perfusion in preeclampsia remains poorly understood. The currently widely accepted model is that failure of proper extravillous trophoblast invasion and remodeling of maternal spiral arteries results in a chronically underperfused placental bed with resulting decreased fetoplacental growth (small placenta and IUGR). The persistence of the smooth muscle cells around basal plate decidual vessels is proposed to result in persistent vasoreactivity to circulating vasoactive mediators and resulting in diminished lumen size and decreased blood flow into the placental intervillous vascular bed. This chronic ischemia can result in the release of additional vasoactive mediators (from fetus and/or placenta) and result in maternal hypertension and preeclampsia. Preeclampsia is defined as maternal hypertension associated with pregnancy after 20 weeks gestation and proteinuria. Preeclampsia is relatively common (2-7% of primigravids), however, 75% of these are only mild cases. Risk factors include primigravida, young age, multiple gestation, history of chronic hypertension, previous preeclampsia, diabetes and thrombophilia. There are paternal risk factors as well. Most recently maternal obesity especially (morbid obesity BMI >40) is associated with an increased risk of preeclampsia. The pathogenesis leading to obesity related adverse effects in pregnancy including preeclampsia remains unclear but the number of obese pregnant women is increasing.

**Pathology:** Probably the most significant pathologic finding associated with chronic maternal vascular underperfusion is small placental size (<10%). The histologic features of maternal vascular underperfusion are shared by all the various etiologies that lead to underperfusion such that it is impossible to distinguish maternal vascular underperfusion due to preeclampsia from that due to antiphospholipid antibody syndrome, etc. We divide the histologic findings that define maternal vascular underperfusion into “vascular lesions” and “villous changes.” The vascular lesions include fibrinoid necrosis (acute atherosis) of maternal (decidual) vessels found in the membranes or at the basal plate. The maternal vessels become surrounded by dense pink material (fibrinoid) and are often associated with acute or chronic inflammation. If clear evidence of foamy macrophages is seen we use the term acute atherosis. This process is, at best patchy, with only scattered vessels affected. The number of affected vessels is
not necessarily associated with the severity of the clinical presentation. This vascular injury is thought to result from vasospasm and diffuse endothelial injury although the molecular details are still being explored. These injured vessels can also contain fibrin thrombi. In thrombophilic states the thrombi may precede the vascular injury. Often associated with thrombosed decidual vessels are areas of decidual necrosis that can have acute inflammation. Another vascular lesion associated with maternal vascular underperfusion includes persistent muscularization of basal plate arteries. Any basal plate artery with smooth muscle cells is abnormal, as these should all be remodeled in the first and early second trimester. Finally hypertrophy of the smooth muscle cells in the membrane decidual arterioles is abnormal and reflective of maternal vascular underperfusion. The criteria for mural hypertrophy of membrane arterioles is that the thickness of the smooth muscle layers must be >50% (some studies used 30%) of the total diameter of the vessel or the vascular lumen is <50% (70% in other studies) of the total diameter (both sides of smooth muscle layers and the lumen together = total diameter). The villous changes associated with maternal vascular underperfusion include villous infarcts. Villous infarcts are quantitated as best as possible and we report the largest size and the total amount (%) of parenchyma affected. We also try to estimate the relative age of the infarcts which is a less than precise process. We report evidence of villous hypermaturation due to chronic underperfusion including increased syncytial knots (Tenney-Parker changes) and distal villous hypoplasia (abnormally small size of the terminal villi for that gestational age). The underperfusion of the intervillous space can also result in local areas with increased perivillous fibrin and villous agglutination. These latter 2 findings are nonspecific, however. The greatest problem with all of these criteria is How much of each criteria is needed to assign the diagnosis of “Findings consistent with maternal vascular underperfusion?” All of the above histologic findings can be found in varying amounts in many placetas that are small, large or normal size. Finally, there is the increased risk of abruption seen in patients with preeclampsia. We report the retroplacental hemorrhages separately and discuss any possible association with maternal vascular underperfusion in a note.

**Clinical associations:** Maternal complications associated with preeclampsia include abruption, DIC, acute renal failure, pulmonary edema, liver failure, stroke and death. Preeclampsia is associated with maternal HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). Fetal complications of preeclampsia include preterm delivery, IUGR, abruption, hypoxic ischemic neurologic injury, and death. Mother’s with severe preeclampsia or eclampsia are delivered as soon as possible as removal of the placenta usually ameliorates the symptoms. However, if a premature neonate will face the usual potential for numerous complications associated with prematurity. The placental underperfusion can also result in a thin umbilical cord, which is predisposed to injury, and can lead to oligohydramnios with potential adverse effects on normal lung development.
V. FETAL VASCULAR OBSTRUCTION

**Background:** The pathogenesis leading to thrombus formation within the fetal vasculature is dictated by Virchow’s triad, whereby thrombi can form as a result of endothelial damage, hypercoagulable states, or turbulent flow with stasis. A number of etiologies can cause one of these processes to be initiated and thereby result in thrombi within the fetal circulation. Possible etiologies include acute chorioamnionitis (this precludes the diagnosis of fetal thrombotic vasculopathy as fetal vascular thrombi can occur as part of an ascending maternal infection or fetal sepsis – a hypercoagulable state), umbilical cord obstruction/accident (can result in local endothelial injury and more significantly stasis of flow), fetal and/or maternal thrombophilia (this is a weak and controversial association), possibly toxic causes (meconium myonecrosis), polycythemia, fetal heart failure, chronic villitis with obliterative vasculitis and others. Overlap of many of the features of involutional changes associated with prolonged intrauterine fetal demise (avascular villi, hemorrhagic endovasculitis, recanalization of stem vessels) can make diagnosis of premortem fetal vascular obstruction difficult in stillborns. Multiple risk factors may be present at one time and contribute to the final placental pathology. The most severe form of fetal vascular obstruction is defined by histologic changes referred to as “fetal thrombotic vasculopathy”. The less severe forms may be best described as “findings consistent with fetal vascular obstruction”. The severity does not necessarily relate to the etiology. Terminology and specific histologic criteria have been established to help categorize this type of placental pathology. What appears to be lacking, as with other forms of placental pathology, are good quantitative criteria for each histologic finding to better assign a specific cause.

**Pathology:** The placenta can be small or normal size. If the obstruction to fetal blood flow is long standing and severe there will be many avascular villi and the placenta is often small for gestational age. The histologic criteria for these lesions are well described (see references listed below). As with maternal vascular underperfusion we divide the histologic findings into vascular lesions.

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**Additional references:**


and villous changes. The vascular lesions that define obstruction to fetal blood flow include thrombi involving chorionic plate or stem vessels as well as thrombi within umbilical cord vessels. These thrombi can be acute and difficult to definitively diagnose or organizing with attachment to the vascular wall. The acute thrombi are often difficult to identify grossly, whereas more remote thrombi are often white and more firm/solid. Vascular ectasia (dilation) is listed as a minimal histologic criterion for diagnosing a possible cord accident in stillbirths with abnormal umbilical cords (Parast and colleagues, see reference below). Mural intimal fibrin thrombi (also known as endothelial cushions) can occur in chorionic and villous stem vessels. These represent non-occlusive intramural fibrin thrombi usually characterized by residual hard-pink fibrin and fibroblast proliferation bulging from the wall into the lumen of a vessel. Long standing cushions can be calcified. Another vascular lesion frequently seen in placentas with fetal vascular occlusion are recanalized chorionic and stem vessel lumens. If associated with extravasated and fragmented red blood cells these recanalized vessels are referred to as hemorrhagic endovasculitis. Recanalized vessels have been the focus of many heated discussions with regards to their true relevance and can occur as a part of involutinal changes associated with intrauterine fetal demise. These are therefore not considered a specific criteria in fetal vascular obstruction. Villous changes include villous stromal-vascular karyorrhexis, which represents an early stage of apoptosis and degeneration of endothelial cells and stromal fibroblasts in response to vascular occlusion upstream. This is usually seen in focal areas associated with obstruction and more diffusely as an involutinal change associated with IUFD. The end result of long standing fetal vascular occlusion are avascular villi. Avascular villi are usually seen in small to large localized collections representing the region with diminished fetal blood flow. They appear as collagenized pink villi without intravillous vessels. Unlike an infarct the syncytiotrophoblast is spared and remains basophilic. In addition, viable stromal cells can also usually be found. The villi are not necrotic but simply avascular. Remember the differential diagnosis of collections of avascular villi includes chronic villitis. The extent of each of the villous changes should be noted. Fetal thrombotic vasculopathy (FTV) is the terminology used to represent the most severe forms of fetal vascular obstruction and is defined by the presence of thrombi (the number is not defined) and significant numbers of avascular villi (>15 avascular villi per slide with at least 3 slides examined (45 total avascular villi)). There remains debate as to the significance of this particular number of affected villi. In general, FTV is characterized by more extreme vascular and villous changes than the less severe forms and pathologists should develop a threshold for specifying FTV using the above criteria as a guideline. In the study by Parast et al., the authors defined the minimal histologic criteria for designating a cord accident as the likely cause of death in stillborns with umbilical cord abnormalities. They defined the minimal histologic criteria to be vascular ectasia and thrombi with either avascular villi or stromal-vascular karyorrhexis in a regional and not diffuse pattern (the exact number of affected villi were not designated). There could not be abruption, infarction or chronic villitis.
**Clinical associations:** Obstruction to fetal vascular flow can result in IUGR, fetal monitoring abnormalities, neurologic injury, hepatic failure, limb infarction, renal vein thrombosis, infarcts in other organs including the GI tract, and intrauterine fetal demise. Fetal vascular thrombi in the setting severe acute chorioamnionitis in very low birth weight infants is a major risk for neurologic impairment.

**Additional references:**


**VI. MISCELLANEOUS PLACENTAL LESIONS**

**A. MASSIVE PERIVILLOUS FIBRIN DEPOSITION (maternal floor infarct):**

**Background:** Increased perivillous fibrin can occur in the setting of maternal underperfusion but then it is usually regional. In massive perivillous fibrin deposition (also known as maternal floor infarction) there is markedly increased perivillous fibrin and extracellular matrix fibrinoid surrounding distal villi in the lower 2/3 of the placenta usually including the basal plate. The etiology is idiopathic but it can recur in future pregnancies (up to 30% reported). There is an increased risk of this disorder in patients with autoimmune diseases, preeclampsia and thrombophilias. This disorder is rare.

**Pathology:** There are two histologic patterns of presentation one being a rind-like basal plate-associated deposition of fibrin and thickening which was originally called maternal floor infarction. The second presentation is diffuse lacy strands of fibrin marbling the lower 2/3 of the parenchyma. Histologically there is extensive intervillous fibrin surrounding but not displacing distal villi with large numbers of associated intermediate trophoblast cells. The entrapped villi can become infarcted due to diminished perfusion. Localized lesions should not be
confused with this more diffuse process. Perivillous fibrin occupying >30-50% of the intervillous space has been proposed to be potentially lethal to the fetus. Care must be taken with stillbirths as increased perivillous fibrin can occur as part of involutional changes.

**Clinical associations:** This is a serious disease that can recur and is associated with recurrent pregnancy loss (both spontaneous abortions and stillbirths), severe IUGR and neurologic impairment. It often begins in late second trimester or early third trimester. If suspected clinically early delivery is recommended. Therapy using anticoagulants remains controversial.

**Additional references:**


**B. CHORANGIOSIS AND CHORANGIOMATOSIS**

**Background:** Chorangiosis is a diffuse increase in the number of villous capillaries in the terminal villi, whereas chorangiomatosis is a multifocal lesion characterized by increased villous capillaries of secondary and tertiary stem villi (often seen in preterm placentas). Chorangiosis occurs in the setting of chronic prenatal hypoxia and is seen in large placentas from diabetics, associated with other maternal chronic disease (severe anemia and preeclampsia), and in placentas delivered at high altitude. It is seen in placentas of smokers and in mothers with chronic hypoxia due to heart disease. Localized chorangiomatosis is associated with preeclampsia, prematurity, and multiple births. Diffuse multifocal chorangiomatosis is associated with IUGR, prematurity, preeclampsia, an enlarged placenta and congenital anomalies. Both of these lesions (chorangiosis and chorangiomatosis) are relatively uncommon.
Pathology: Chorangiosis usually involves only the distal villi and the increased capillaries are lined by endothelium. The rule of tens apply for the diagnosis: there needs to be 10 or more villous capillary cross sections seen in 10 or more villi in clusters in several (10) fields using a 10x objective in 3 different noninfarcted areas of the placenta (diffuse involvement). Often there will be 15-20 capillary cross-sections in some capillaries. The most difficult differential diagnosis is when there is marked vascular congestion in an otherwise normal term placenta. The distinction can be nearly impossible at times. Some pathologists use the terms focal chorangiosis or borderline chorangiosis in equivocal cases. Chorangiomatosis has 2 patterns. Localized chorangiomatosis involves a focal or segmental area of adjacent villi with increased vessels and cellularity of stem villi, whereas diffuse multifocal chorangiomatosis involves multiple independent areas of the placenta.

Clinical associations: Chorangiosis is associated with perinatal morbidity (cerebral palsy) and mortality and is probably a marker for chronic hypoxia. Chorangiomatosis has similar associations with hypoxic states and is increased in patients with Beckwith-Wiedmann syndrome and with other congenital anomalies.

Additional references:


C. CIRCULATING NUCLEATED FETAL RED BLOOD CELLS

Background: Increased numbers of circulating nucleated fetal red blood cells is indicative of fetal hypoxic/ischemic stress. The finding is nonspecific for etiology but is extremely helpful in an effort to determine whether there was fetal hypoxic stress in utero prior to delivery. In the third trimester there should be essentially no circulating nucleated fetal red blood cells. The presence of these cells indicates premature release of red cell precursors from the bone marrow and/or if chronic, indicates increased fetal erythropoiesis. Increased circulating fetal red blood cells can be seen in association with several of the placental pathologies.
already discussed (maternal vascular underperfusion, massive perivillous fibrin deposition, severe fetal thrombotic vasculopathy) but in addition nucleated fetal red blood cells are commonly seen in fetuses with anemia for any reason (Rh or ABO incompatibility, fetomaternal hemorrhage, many others).

Pathology: Nucleated fetal red blood cells can be difficult to distinguish from fetal lymphocytes especially if the placental tissue is poorly preserved or not adequately fixed. Once identified as nucleated red blood cells within the fetal circulation an effort should be made to quantitate the numbers as mild, moderate, or severe. We use the method of examining the distal villi at 40X and counting the number of nucleated RBCs. A mild increase is defined by 2-3 unequivocal nucleated fetal red blood cells in one or more terminal villi in 3 or more 40X fields. Moderate increase is greater than 3 nucleated red blood cells in one or more terminal villi in 3 or more 40X fields. A marked increase is defined as clusters of nucleated red blood cells and immature erythroblasts in most 40X fields. Cases of severe anemia are more likely to have a marked increase in the number of circulating nucleated fetal red blood cells.

Clinical associations: Increased nucleated fetal red blood cells in the circulation indicates fetal hypoxia, but this does not identify the etiology. The time interval necessary to see increased circulating nucleated fetal red blood cells after the hypoxic event remains controversial although most individuals believe it takes several hours (2-24 hours). Dr. Redline has indicated that a marked increase in nucleated fetal red blood cells in an otherwise normal fetus probably takes 6-12 hours to develop. One cause for fetal hypoxia that can occur acutely in term fetuses and result in increased nucleated fetal red blood cells is a significant fetomaternal hemorrhage. This can only be definitively diagnosed by flow cytometry or the Kleihauer-Betke test run on maternal blood. The half-life of fetal blood cells in the maternal circulation is about 100 days (less if there is blood group incompatibility) so this test can be ordered several days following delivery. Several nonspecific placental findings can be supportive of the diagnosis of fetomaternal hemorrhage including increased circulating nucleated fetal red blood cells, placental edema, and intervillous thrombi. Intervillous thrombi represent sites of fetomaternal hemorrhage, but they are very common and most do not reflect a large fetomaternal hemorrhage. Multiple or large intervillous thrombi increase the probability of a significant fetomaternal hemorrhage. The result of a large fetomaternal hemorrhage is severe fetal anemia with associated congestive heart failure, CNS injury, hydrops, and/or death.

Additional references:


D. MECONIUM

Background: Hypoxic stress in utero in the late third trimester can result in the passage of meconium into the amniotic fluid. The trigger in many cases is thought to be transient umbilical cord obstruction which is common in late pregnancy. Meconium represents the fetal stool and is composed of bile acid, phospholipases and other components. Meconium can have detrimental effects on umbilical and chorionic plate blood vessels. Multiple factors can alter the toxic effects of meconium including the amount passed, the duration of exposure and the volume of the amniotic fluid. Meconium passage and the presence of chorioamnionitis often coexist and can likely synergize to lead to vascular injury. Meconium passage at or after term is common (affecting 15-20% of all placentas). Prior to 34 weeks gestation meconium passage is seldom seen.

Pathology: Grossly meconium passage can result in deep green discoloration of the chorionic plate and membranes or to just mild discoloration/opacification of the membranes. Meconium passage can result in toxic effects on the amnion resulting in cytoplasmic vacuolization, reactive changes (change from cuboidal to tall columnar morphology), edema, or even amniocyte necrosis. The meconium is picked up by tissue macrophages and appears as red-yellow-tan pigment within vacuolated macrophages in the amnion, chorion, extravillous trophoblast layer or decidua, dependent upon the duration of exposure. The differential diagnosis of this brown tinged pigment includes hemosiderin, which can be assayed by iron stains. Determining the duration of meconium passage in utero is an inexact science with studies showing disparate results. Estimates from one study indicates that it takes about 1 hour for meconium to begin to accumulate in the amnion. Spread through the superficial chorion likely takes 3 or more hours and for the pigmented macrophages to reach the deeper layers of the chorionic plate and/or invade Wharton’s jelly (with resulting green umbilical cord) may take as long as 12-16 hours. One of the known detrimental effects of prolonged meconium exposure is resulting focal necrosis of the smooth muscle cells surrounding the umbilical cord vessels, referred to as myonecrosis. This is
characterized by rounding up of the smooth muscle cells with cytoplasmic hypereosinophilia and pyknosis of the nuclei with eventual loss of nuclear basophilia of the smooth muscle cells surrounding one or more of the umbilical vessels (usually one of the arteries).

**Clinical associations:** Meconium passage is thought to be indicative of some degree of hypoxic/ischemic stress but it is nonspecific. Meconium is most commonly seen in fetuses without any other signs of fetal distress. Many fetuses that have undergone serious intrauterine stress do not pass meconium. However, meconium associated umbilical vessel myonecrosis has been associated with adverse CNS outcomes. Meconium passage also predisposes the affected neonate to possible meconium aspiration syndrome, however, there are no predictive findings within the placenta to identify the subgroup of neonates that will develop this complication.

**Additional references:**


**E. CHRONIC DECIDUITIS WITH PLASMA CELLS**

**Pathology:** The decidua at the basal plate or associated with the membranes can contain increased numbers of lymphocytes, macrophages, and plasma cells. The presence of lymphocytes and macrophages are usually considered non-pathologic. However, the presence of plasma cells is always abnormal. How many plasma cells (1, 2, etc.) are needed to consider them pathologic, remains to be determined. Some pathologists consider even one plasma cell pathologic.

**Clinical associations:** While increased chronic inflammation in the decidua is non-specific (lymphocytes and macrophages are common), the presence of plasma cells should raise concern for a possible chronic maternal infection (possible chronic endometritis). This is not a 100% association (closer to about
30%). Chronic deciduitis with plasma cells often, but not always, accompanies chronic villitis.

**Additional references:**


**F. PLACENTAL EDEMA**

**Background:** Patchy villous edema can be seen in association with many of the placental pathologies already discussed including chorioamnionitis, maternal vascular underperfusion, cytogenetic abnormalities, and others as well as in placentas with no other pathology. Severe villous edema known as a hydropic placenta and is less common.

**Pathology:** Microscopically the villous stroma is edematous (clear whitespaces) and villi appear enlarged. There can be syncytiotrophoblast cell necrosis, villous capillary lumens may be reduced, and Hofbauer cell number may be increased. Increased circulating nucleated fetal red blood cells may be present. Usually villous edema is easily assessed and it is important to determine the extent of involvement (mild, moderate, severe). Some very rare inborn errors of metabolism can mimic edema. However, in many storage diseases the inclusions also occur in an intracellular manner, often affecting the trophoblast cells.

**Clinical associations:** The etiology of the edema is important to consider but the differential diagnosis is extremely broad including chorioamnionitis, genetic disorders, fetomaternal hemorrhage, congenital heart disease, other infections (parvovirus), and many more. It can be helpful to establish whether there is also fetal/neonatal edema. The finding of villous edema is usually nonspecific and in the absence of placental evidence of chorioamnionitis the etiology is often not identified from placental examination alone.

**Additional references:**


G. ABERRENNT IMPLANTATION (placenta accreta, increta and percreta):

Background: Placenta accreta represents abnormal implantation characterized by failure of normal decidua to form with resulting insertion of chorionic tissue directly into the myometrium. Placenta accreta occurs when chorionic tissue is directly attached to myometrium without intervening decidua. Placenta increta represents deeper invasion of the myometrium by villi, and placenta percreta is when the placental villi have penetrated the uterine wall (serosal surface). The true defect here is deficiency of decidua and not the direct contact of villi with myometrium. Normally the presence of decidua seems to prevent deep invasion of the myometrium by the extravillous trophoblast. Focal placenta accreta is probably much more common than previously reported with the newer definition of myometrium in direct contact with chorionic tissue (fibrinoid layers or extravillous trophoblast) without intervening decidua. The incidence of accretas is rising and this is probably due, at least in part, to the newer definition and the increasing incidence of cesarean sections. The risk factors for the development of accreta is prior cesarean section (resulting in scar tissue deficient in endometrium for decidualization after pregnancy is initiated), prior endometrial curettage, and placenta previa (insertion over the cervical os). Other risk factors include submucosal leiomyomas and uterine anomalies.

Pathology: Normal separation of the placenta from the uterus occurs just peripheral to Nitabuch’s fibrinoid layer along the decidua. In the absence of decidua the separation plane is incomplete and the placenta may bleed or be partially retained. A missing cotelydon due to focal placental accreta should be reported if accurately assessed grossly. Histologically it is the absence of decidua that defines the pathology. As stated above chorionic elements in direct contact with myometrium without intervening decidua is the definition of placenta accreta and this can be very focal, multifocal or diffuse. Difficulty can arise in misdiagnosing extravillous trophoblast cells as decidua and visa versa. Overdiagnosis can occur if deeply penetrating placental-site giant cells are interpreted as accreta. Placental-site giant cells normally invade the myometrium. It is common to find myometrial fibers attached to the basal plate with intervening decidua and although this is not associated with an adverse outcome, it is abnormal and we report it.

Clinical association: Placenta accreta is associated with an increased risk of retained placenta, pre- or post-partum hemorrhage, and uterine rupture in the setting of increta or percreta. Older studies report life threatening hemorrhage with maternal and/or fetal death in 9-10% of cases of placenta accreta. These most likely represented near complete accreta and not the focal accreta seen more commonly now. The treatment of increta and percreta is cesarean delivery followed by hysterectomy.
**Additional references:**


**H. CHRONIC (HISTIOCYTIC) INTERVILLOSITIS (massive chronic intervillostis)**

**Background:** Chronic histiocytic intervillositis is defined histologically as a diffuse infiltration of the intervillous space by a monomorphic population of CD68 positive histiocytes accompanied by increased perivillous fibrinoid and extravillous trophoblast. The villi are not involved by the histiocytes (this is not a villitis). This lesion occurs more commonly in spontaneous abortions (about 10 per 1000) especially in the first trimester and is rare in later pregnancy (<1 in 1000). The incidence is reported to be much higher in women with recurrent spontaneous abortions (80 per 1000). The differential diagnosis includes placental malaria, which is exceedingly rare in the US. The etiology remains unknown.

**Pathology:** The placentas involved by chronic histiocytic intervillositis are usually small for gestational age. The histologic findings as described above define this entity. If chronic villitis or a polymorphous intervillous inflammatory infiltrate is present then this entity is excluded. Malaria should be considered with the clinical history reviewed and malaria organisms should be sought (only present in 40% of infected placentas) as well as the black malaria pigment (only present about 35% of the time). A note should probably be added that malaria cannot be excluded based on the absence of diagnostic findings.

**Clinical associations:** Chronic histiocytic intervillositis is associated with recurrent spontaneous abortion, IUGR, and intrauterine fetal demise. Overall perinatal mortality rate has been reported to be as high as 77%. The death rate is lower in the third trimester (18%). A recent review of treatments for this disorder failed to show any significant improvement in outcome with treatment and there was a small trend (not statistically significant) that treatment resulted in a lower incidence of live birth than no treatment.

**Additional references:**

I. EOSINOPHILIC/T-CELL VASCULITIS

**Background:** Eosinophilic/T-cell vasculitis (ETV) is an unusual and rare (0.2 to 0.6% of placentas) entity first described in 2002. ETV consists of a fetal derived chronic inflammatory infiltrate composed of eosinophils and CD3 positive T-lymphocytes that focally involves a single chorionic artery or vein. Additional sampling of involved placentas has failed to reveal additional involved vessels. Neutrophils are not a component of the inflammation. The vast majority of cases involve term placentas and the remainder of cases are 34 weeks gestation or older. Most cases have a maternal or fetal abnormality, likely leading to the placental examination, however, a consistent pattern of abnormalities has not been observed. The etiology remains unknown. Recurrences in subsequent pregnancies have not been observed.

**Pathology:** The pathologic findings are as described above. There is no obvious gross lesion and usually only a single vessel is involved by inflammation composed of eosinophils and T-lymphocytes. In about 10-15% of cases there can be an associated intraluminal thrombus. The most recent study of 51 placentas with ETV showed a statistically significant association of ETV with villitis of unknown etiology (43% of ETV cases versus 13% of control cases had chronic villitis), although most of the cases were low grade in both groups. In addition, ETV was associated with fetal vascular obstructive disease in 23% of cases compared to 11% in controls. Other placental lesions failed to show statistically significant differences between placentas with ETV and controls.

**Clinical associations:** The clinical significance, if any, has not yet been observed. Thus far, ETV is not associated with known adverse outcomes although only a few studies have been performed and long term followup is lacking.

**References:**

VII. TEMPLATES USED AT NORTHWESTERN

Placental Gross Description

Received (fresh/fixed) labeled with the patient’s name and “______” is a (ovoid/irregular shaped/bilobed) placenta with attached membranes and umbilical cord. The membranes are (intact/ruptured) and the site of rupture is (# cm from the edge). Membranes are inserted (at the margin/circummarginate (% of circumference involved and greatest amount (in cm) of extrachorialis). The membranes are (clear/opaque/green/other). The umbilical cord is inserted # cm from the margin and insert (normally/velamentously/furcated). The umbilical cord measures # cm in length and averages # cm in diameter. The external surface of the umbilical cord is (unremarkable/with amnion nodosum/white lesions) and there are # twists per 10 cm segment. The cut surface shows # vessels. Trimmed weight of the placenta is # grams and the disc measures __X__X__ cm. The fetal surface is (color/lesions). The maternal surface is (color/lesions/intact). Cut surface shows (beefy red parenchyma/lesions). Representative sections are submitted as follows:

1. membrane rolls (2-3 rolls per cassette)
2. umbilical cord (2-3 pieces per cassette)
3. maternal surface biopsies (3 biopsies in one cassette)
4. full thickness parenchyma
5. full thickness parenchyma

additional sections lesions/abnormalities
General Templates

**PLWT**  **PLACENTA, DELIVERY:**
- PLACENTAL WEIGHT, # GRAMS, SMALL/LARGE/APPROPRIATE FOR GESTATIONAL AGE (EXPECTED AT (GESTATIONAL AGE) # GRAMS).

**BPMYO**  BASAL PLATE WITH ATTACHED MYOMETRIAL FIBERS.

**CDPC**  CHRONIC DECIDUITIS WITH PLASMA CELLS.

**MEMHEM**  MEMBRANES WITH REMOTE PARIETAL DECIDUAL HEMORRHAGE WITH HEMOSIDERIN.

**MEC**  (MILD/MODERATE/NUMEROUS) MECONIUM-LADEN MACROPHAGES IN (AMNION/CHORION/DECIDUA/AT CHORIONIC PLATE).

**TERMGEST**  VILLOUS MATURATION CONSISTENT WITH TERM GESTATION (OR APPROPRIATE FOR GESTATIONAL AGE).

**MEMB**  MEMBRANES AND UMBILICAL CORD WITHOUT SIGNIFICANT ABNORMALITY.
Amnionic Fluid Infection

- FINDINGS CONSISTENT WITH ACUTE AMNIONIC FLUID INFECTION:
  - MATERNAL INFLAMMATORY RESPONSE, STAGE ____.
  - MEMBRANES WITH
    Pick one:
    - ACUTE MARGINATING CHORIODECIDUITIS.
    - ACUTE CHORIOAMNIONITIS.
    - ACUTE NECROTIZING CHORIOAMNIONITIS.
  - CHORIONIC PLATE WITH
    Pick one:
    - ACUTE SUBCHORIONITIS
    - ACUTE SUBCHORIONITIS AND CHORIONITIS.
    - ACUTE SUBCHORIONITIS, CHORIONITIS, AND AMNIONITIS.

- FETAL INFLAMMATORY RESPONSE, STAGE ____.
  Pick all that apply:
  - ACUTE CHORIONIC VASCULITIS.
  - ACUTE UMBILICAL PHLEBITIS.
  - ACUTE UMBILICAL ARTERITIS.
  - ACUTE UMBILICAL PANVASCULITIS WITH FUNISITIS.
Maternal Vascular Underperfusion

- FINDINGS CONSISTENT WITH MATERNAL VASCULAR UNDERPERFUSION.
  - VASCULAR LESIONS:
    - ACUTE ATHEROSIS/FIBRINOID NECROSIS OF BASAL PLATE OR MEMBRANE ARTERIOLES.
    - PERSISTENT MUSCULARIZATION OF BASAL PLATE ARTERIES.
    - MURAL HYPERTROPHY OF MEMBRANE ARTERIOLES.
  - VILLOUS CHANGES:
    - VILLOUS INFARCTS, ACUTE/SUBACUTE/REMOTE, __CM, MULTIPLE OCCUPYING __% OF PARENCHYMA.
    - INCREASED SYNCYTIAL KNOTS.
    - DISTAL VILLOUS HYPOPLASIA.
    - VILLOUS AGGLUTINATION.
    - INCREASED PERIVILLOUS FIBRIN.
FINDINGS CONSISTENT WITH CHRONIC FETAL VASCULAR OBSTRUCTION (INCLUDES FETAL THROMBOTIC VASCULOPATHY).

- VASCULAR LESIONS:
  - THROMBI INVOLVING CHORIONIC PLATE VESSELS/STEM VESSELS.
  - ACUTE/SUBACUTE/REMOTE MURAL INTIMAL FIBRIN THROMBI (ENDOTHELIAL CUSHIONS), CHORIONIC PLATE VESSELS/STEM VESSELS.
  - RECANALIZED LUMENS, CHORIONIC PLATE/STEM VESSELS.

- VILLOUS CHANGES:
  - VILLOUS STROMAL-VASCULAR KARYORRHEXIS.
    - EXCLUSIVELY SMALL FOCI.
    - VARIABLY SIZED FOCI.
  - AVASCULAR VILLI.
    - EXCLUSIVELY SMALL FOCI.
    - VARIABLY SIZED FOCI.
    - GREATER THAN 45 AVASCULAR VILLI (3 FOCI OF MORE THAN 15 VILLI EACH).
Chronic Villitis

- FOCAL/MULTIFOCAL LOW GRADE CHRONIC VILLITIS OR PATCHY/DIFFUSE HIGH GRADE CHRONIC VILLITIS.
  - NO VIRAL INCLUSIONS SEEN.
  - IMMUNOHISTOCHEMICAL STAIN FOR CYTOMEGALOVIRUS (CMV) IS NEGATIVE. (OPTIONAL)
  - AVASCULAR VILLI.
  - CHRONIC DECIDUITIS WITH PLASMA CELLS.
  - OBLITERATIVE ARTERITIS IN VESSELS OF TERMINAL/STEM VILLI.
  - SCATTERED GRANULOMATOUS INFLAMMATION SEEN.
  - FOCAL CHRONIC CHORIONITIS.
  - ASSOCIATED PATCHY CHRONIC INTERVILLOSITIS.
  - SEE NOTE.

Note: Chronic villitis, although inflammatory, is associated with infection in only a small number of cases. In these instances, the most common infections are T. gondii, CMV, or syphilis. However, most of the time the inflammatory process is not associated with infection and is termed “villitis of unknown etiology.” High grade patterns of chronic villitis are associated with an increased risk of fetal growth restriction or fetal demise, and may recur in future pregnancies.
Abruption Note:

In case of clinical suspicion of abruption without retroplacental or marginal hemorrhage the following NOTE can be added.

Note: While there is no gross or histologic evidence of abruption, it should be noted that acute abruption may show no pathologic findings on placental examination as the clot forms acutely without time to attach to the maternal surface, indent, or infarct the placental parenchyma.

I do not routinely use the term “ABRUPTION” in the diagnostic line, as this is really a clinical term. I describe the hemorrhage in the diagnostic line and often add a NOTE.

ACUTE/SUBACUTE/REMOTE RETROPLACENTAL/MARGINAL/PARENCHYMAL HEMORRHAGE (____ CM IN GREATEST DIMENSIONS).

Note:
The described hemorrhage is consistent with the clinical history of abruption. OR
The significance of the described hemorrhage is unknown. Clinical correlation may be helpful.