1. PLACENTAL SPECIMEN ORIENTATION

Placental disc

Basal palate (maternal surface) and chorionic plate (fetal surface)

Fetal (chorioamniotic) membrane and umbilical cord

2. CIRCULATORY PROBLEM

Decidual vasculopathy: A group of related pathology in the decidual arteries (lack of physiologic conversion, hypertrophic decidual vasculopathy, atherosclerosis and thrombosis). It can be found in maternal hypertension, preeclampsia, autoimmune diseases, and infants with small for gestational age. Acute atherosis occurs in all cases of preeclampsia. However, all placentas with acute atherosis do not necessarily cause maternal hypertension.

Infarction: A localized region of ischemic necrosis of villi. However, small infarcts of less than 3 cm in diameter are commonly found in uncomplicated pregnancies. Failure of utero-placental blood flow is the major cause; usually resulting from insufficient spiral arterial perfusion pressure owing to luminal narrowing or occlusion.

Hematoma and placental abruption: Accumulation of blood clots; recent or chronic. Placental abruption (abruptio placentae) refers to the clinical presentation in the mother of premature placental separation due to retroplacental hematoma. The clots of retroplacental hematoma situate between the placental floor and uterine surface giving a maternal symptoms of pain, bleeding, and progressive accelerated uterine enlargement. The two terms are often used interchangeably, leading to confusion between clinical diagnosis and pathologic lesion. Except subamniotic hematoma which is though to be fetal blood in origin following rupture of fetal vessel in the chorionic plate, most of the blood in hematomas (intraplacental, subchorial, retroplacental, marginal) is maternal. The prognosis is depended on how much of the involvement and which location that hematomas situate.
**Massive perivillous fibrin deposit (MPFD) and Maternal floor infarction (MFI):**
Uncommon placental abnormalities of unknown pathogenesis, characterized by excessive accumulation of amorphous fibrinoid material encasing chorionic villi. The proposed mechanisms of MFI are varied and include stasis or inadequate drainage of the intervillous space (sometimes due to changes in intrauterine hydrostatic pressure gradient), inappropriate extravillous trophoblastic cell proliferation and trophoblastic cell damage by maternal autoantibodies. Any of these processes may stimulate excessive fibrinoid deposition. By definition, the fibrinoid deposition is confined to basal villi along the decidual basalis in MFI, whereas the deposition is more widely distributed throughout the placenta in MPFD and may even be transmural. However, both conditions overlap since the distribution of fibrinoid material is not always distinctively different in some cases; suggesting MFI and MPFD are different manifestations of the same condition. The amorphous material that embeds villous structure is appears to be a combination of serum fibrin from coagulation cascade (fibrin type-fibrinoid) and fibrin-like, trophoblast-derived extracellular substance (matrix type-fibrinoid). For MFI, a thickness of at least 3 mm, evident on at least one slide, is required for diagnosis. MPFD is implied involvement of at least 50% of the villi as seen on at least one slide.

**Fetal thrombotic vasculopathy (FTV):** Chronic placental disorder involving the villous ramification secondary to upstream chorionic or stem vessel thrombo-occlusive events. Affected groups of contiguous terminal villi showed involution of the stromal capillaries with formation of avascular villi. The exact etiology is controversial and proposed mechanisms include activation of the fetal coagulation system and alterations in fetal-placental circulation. Early changes include villous stromal and/or endothelial karyorrhexis and later changes include loss of capillaries with stromal hyalinization. Reporting systems as follows haven’t been accepted yet, but it is a step forward in the standardization. The diagnosis includes: 1) presence or absence of large vessel thrombosis and 2) the grading of avascular villi (grade 1: <15 affected villi/slide; grade 2: ≥15 affected villi/slide). Clinical associations with FTV include fetal and/or maternal thrombophilia, maternal diabetes and umbilical cord obstruction. Adverse perinatal outcomes include IUGR, discordant growth in twins, birth asphyxia, thromboembolism and cerebral palsy.
3. INFLAMMATION AND INFECTION

Although the causes of inflammatory lesions of the placenta are uncertain in minority of cases, infections are the main etiology of placental inflammation in daily practice. Organisms may reach the placenta and fetus by a variety of routes including 1) ascension (from the vagina/cervix/decidual), 2) maternal bloodstream, 3) direct introduction (amniocentesis/chorionic villous sampling/amnioscopy/percutaneous cord blood sampling) and 4) direct extension from infection from the endometrium. One of the first two routes is common in perinatal infection. The details are discussed below.

**Infectious Related Inflammatory Lesions**

**Acute chorioamnionitis:** It is an important cause of perinatal morbidity and mortality, including adverse long-term neurological outcome and cerebral palsy. The incidence is inversely proportional to gestational age and most cases are due to bacteria or mycoplasma that break through the normal barrier at the cervical os and gain access to the amniotic cavity. This entity, also called “amniotic sac infection syndrome”, is defined histologically by neutrophilic infiltration in the placenta, umbilical cord, and membrane in response to ascending infection. Histologic chorioamnionitis remains the gold standard for the diagnosis, but it correlates poorly with clinical chorioamnionitis, often diagnosed by maternal PROM, fever, leukocytosis during labor.

Microscopic findings are composed of maternal and fetal inflammatory responses. Although maternal response (chorionic plate and membranous chorioamnion inflammation by maternal neutrophils) is used to establish diagnosis by most pathologists, recent data regarding adverse pregnancy outcomes demonstrates the important of fetal inflammatory response (vascular inflammation in the chorionic plate and umbilical cord by fetal neutrophils).

Subcommittee of the Society for Pediatric Pathology-Perinatal Section has been proposed the following systems (the stage for duration and the grade for duration). The stages of maternal inflammatory response are composed of: stage 1 (early), acute subchorionitis and/or acute chorionitis; stage 2 (intermediate), acute chorioamnionitis; stage 3 (late), necrotizing chorioamnionitis. The stages of fetal inflammatory response include: stage 1 (early), chorionic vasculitis and/or umbilical phlebitis; stage 2 (intermediate), umbilical cord arteritis; stage 3 (late), necrotizing funisitis or concentric
umbilical perivasculitis. For histologic grading whether maternal or fetal inflammatory response, it is simply divided as grade 1 and 2 (severe). The histologic features of grade 2 are intense inflammatory cell infiltrations or abscess formations.

**Subacute chorioamnionitis:** The histopathology shows mixed mononuclear cells and degenerating neutrophils in the chorionic plate. The proposed etiology is either ascending infection by organisms of low virulence or repetitive bouts of mild infection in pregnant women with repetitive second and third trimester vaginal bleeding. In contrast to acute chorioamnionitis, inflammatory cells are most numerous in the amnion and upper chorion rather than subchorionic fibrin and lower chorion.

**Acute chorioamnionitis with peripheral funisitis:** Besides acute chorioamnionitis, this entity is recognized as triangular-shaped microabscess on the surface of the umbilical cord. The abscesses are slightly raised and well-circumscribed yellow-white plaques with 1- to 2- mm in diameter. Most cases have been reported in association with Candida, so the specificity of peripheral funisitis as an indicator of congenital candidiasis is high. Within the abscesses, there are numerous neutrophils admixed with budding yeasts with/without pseudohyphae. The associated fetal inflammatory response is common and necrotizing funisitis is frequent.

**Acute intervillositis:** It is characterized by intervillous neutrophilic infiltrations. The inflammation is usually severe enough to form intervillous abscess and even so-called septic infarct. Chorioamnionitis is a common accompanying feature. *Listeria monocytogene, Staphylococcus aureus* and *Mycobacterium tuberculosis* are the common causative organisms in this circumstance. For *L. monocytogene*, after contaminated food ingestion, bacteria are phagocytosed by intestinal epithelial cells and shed into the feces. Placental infection can occur by both hematogenous and ascending routes. Bacterial spreading to fetus is rapid and common, leading to disseminated granulomas and abscesses throughout visceral organs, called granulomatosis infantiseptica.

**Acute villitis:** It can be diagnosed by neutrophilic infiltrates in the fetal capillaries and stroma of the distal villi, indicating fetal sepsis in utero. *Escherichia coli* and streptococci are common causative organisms in this setting. Acute inflammatory cells often accumulate beneath the trophoblast basement membrane. Most cases are accompanied by chorioamnionitis.
Active chronic villitis: By definition, there are mixed inflammatory cells infiltrating in the villous stroma and adjacent intervillous space. Accompanying features include fetal stem villous vasculitis and villous necrosis, but acute chorioamnionitis is not generally present. The etiology includes either infection (esp. nonsyphilitic spirochetes, some gram-negative bacteria and herpes simplex viruses) or fulminant idiopathic chronic villitis (see below).

Chronic placentitis of TORCH type: Regardless of chronic villous inflammation, the shared placental pathology of TORCH type shows two different patterns, either histiocytic (Hofbauer cell)-predominant villitis (relatively large pale placentas with villous hydrops) or fibrosclerosing villitis (relatively firm placentas with villous fibrosis). The incidence is varied and clinical manifestations are depended on the individual infectious organisms. Histopathologic characters of congenital syphilis are composed of histiocytic-predominant villitis, proliferative endovasculitis and necrotizing umbilical periphlebitis are three essential histologic appearances. A band of eosinophilic precipitate and necrotic debris extending from the umbilical cord periphlebitis is characteristic for syphilis. In addition, umbilical cord is the best location of the placenta to demonstrate spirochetes by special stains. Besides pathognomonic basophilic inclusions in congenital CMV infection, prominent villous stromal plasma cell infiltrates and fibrosis are commonly found. Further evaluation by immunohistochemistry or molecular methods for CMV is strongly recommended in plasma cell-rich placentas.

Perinatal infections with minimal or no placental inflammation: Fetoplacental transmission in these circumstances is rare. Possible mechanisms include phagocytosis by Hofbauer cells, direct contact following villous epithelial denudation and receptor-mediated by the syncytiotrophoblast. Organisms may be found in the intervillous space or syncytiotrophoblast associated with fibrin and necrosis, but little or no inflammatory response. Parvovirus B19, HIV, hepatitis viruses and enterovirus, rubeola virus (measles), Schistosoma sp and C. neoformans are examples.

Idiopathic Inflammatory Lesions

Chronic chorioamnionitis: The incidence is rare and the etiology is unknown. It is, however, frequently found in association with villitis of unknown etiology (discuss
below) or with evidence of longstanding ascending infection. Premature labor and delivery are common associated clinical findings.

**Chronic villitis (Villitis of unknown etiology; VUE):** The incidence of chronic villitis occurs in 5-10% of all placentas. It is associated with IUGR, high recurrence rate and poor perinatal outcome, including fetal demise. Two suggestions have been made with respect to its etiology; infectious disease with not yet recognized agent or immune reaction. The latter concept is supported by presence of maternal T-lymphocytes from the inter villous space infiltrating into villous parenchyma. The placentas with VUE are usually smaller and stiff. Microscopic findings show infiltration of histiocytes and lymphocytes, esp. in the basal villi, with or without villous destruction.

**Chronic (histiocytic) intervillositis (Massive chronic intervillositis):** Diffuse infiltration of the intervillous space by a monomorphic population of monocyte-macrophages. It is commonly associated with recurrent spontaneous abortions, fetal growth restriction and intrauterine fetal death, but much less common in the second and third trimester. Placentas are often small for gestational age. The overall perinatal mortality rate is high. The suggested etiology is inappropriate expression of adhesion molecules on the syncytiotrophoblast secondary to some inflammatory cytokines as well as maternal autoimmune diseases and immunosuppressive therapy. This entity must be distinguished from chronic intervillositis associated with malaria the etiology of which is a specific immune response to erythrocytes parasitized by *P. falciparum* that are sequestered in the intervillous space. Intervillositis and parasite load are greatest in the late second and early third trimesters.

**Chronic deciduitis:** The entity is characterized by either the presence of plasma cells or diffuses chronic inflammation without plasma cells. Focal or multifocal inflammation without plasma cells is excluded from this category. The association of chronic deciduitis and VUE is strong; suggestive of immune response to fetal antigens. However, chronic deciduitis sometimes is found with acute chorioamnionitis in preterm placentas, suggesting subclinical bacterial endometritis.

4. **FETAL (CHORIOAMNIONTIC) MEMBRANE**

**Meconium staining:** Meconium is the earliest stools of an infant. It is almost sterile and normally stored in the infant's intestines until after birth, but sometimes it is expelled into
the amniotic fluid prior to birth or during labor and delivery owning to fetal distress. Microscopically, meconium shows brownish intracytoplasmic granules in macrophages. They are must be differentiated from hemosiderin-containing macrophages, which are associated with previous bleeding. Meconium that stains the fetal surface (chorionic plate) of a placenta are engulfed by histiocytes and subsequently appears as meconium-laden macrophages in the superficial amnion and in deeper chorionic macrophages within 1 hour and 3 hours after exposure, respectively. The amniotic epithelium may become vacuolated and ultimately necrosis. After prolong period of exposure (>16 hours), toxic substances in the meconium can induce necrosis of vascular smooth muscle of umbilical cord and chorionic vessels. In addition, meconium-associated vascular necrosis is significantly correlated with infants with cerebral palsy.

**Squamous metaplasia:** Focal patches of mature keratinizing squamous epithelium. It can be found on the surface of umbilical cord, in particular near the cord insertion. There is no any correlation with adverse pregnancy outcome.

**Amnion nodosum:** Yellow-brown granules comprising a circumscribed heterogeneous matrix of eosinophilic debris, adhering to the chorionic matrix. It is in association with severe oligohydramnios.

**Amniotic bands:** Strips of detached amnion that may wrap and constrict fetal appendages, resulting in amputation.

5. **UMBILICAL CORD**

**Umbilical cord accident:** It is a non-specific term and refers to any problem of the cord resulting to compromised blood flow to baby through the cord. **Cord coiling, torsion and stricture:** Cord is usually coiled, twisted and spiraled, more often in a left twist direction in ratio of ~4:1. Coiling index (numbers of coiled/ cord length) has been used to evaluate the degree to twisting, with an average of 0.21/cm. Non-, hypo-, hypercoiled cords are associated with adverse perinatal outcomes. **Cord length:** Fetal movement is believed to have an influence on the length of cord. Hypoactive fetuses are associated with short umbilical cord, whereas hyperkinetic fetuses are associated with long cord. Short cord usually defined as a length that is shorter than 32-35 cm, whereas long cord length variably defined as greater than 70-100 cm. Abnormal length of umbilical cord is generally associated with adverse pregnancy outcomes, in particular thrombosis and
neurological handicaps. **Cord diameter:** A thin cord is defined as a cross-sectional area less than the 10th percentile due to decreased or absent fluid content of Wharton jelly. It is associated with lower coiling index and reduced umbilical vein flow. In contrast, increased cord diameter because of more jelly has been associated with better fetal outcome. **Cord knots:** True knots, in particular tight true knots, cause Wharton jelly compression at the site of knotting together with venous stasis, leading to thrombosis of the chorionic vessels or even umbilical veins. Whereas true knots are strongly related to poor obstetric outcomes, no clinical important has been noted for false knots because of their structure of just locally redundancies of umbilical vessels, mostly the vein. **Cord entanglement and prolepses:** Profound pathological changes include hemorrhage or even rupture at the site of compression as well as thrombosis in some cases. However, these lesions are not pathognomonic. Clinical findings are needed for interpretation.

**Insertion anomalies:** *Velamentous insertion*-The cord inserts into the fetal membranes rather than on the placental disc. *Marginal insertion*-The cord inserts at the edge of placental disc. *Furcated insertion*-The cord loses Wharton jelly before insertion. Insertion anomalies may affect umbilical blood flows with secondary placental insufficiency and adverse fetal outcomes.

**Umbilical cord vessels:** Single umbilical artery is common. Whether it is due to primary aplasia or secondary atrophy has been debated. It is associated with many congenital malformations as well as low birth weight.