Excerpts from

THE PLACENTA: TO KNOW ME TO IS LOVE ME

What you don't see might hurt the fetus!

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In so many areas of anatomic pathology, what you see is pretty much what you get. Sure the microscopic examination might clarify a tumor type or identify a source of infection, but often there are no surprises. Not so with the placenta. A placenta that "looks normal" may in fact show microscopic abnormalities suggesting acute or chronic intrauterine hypoxia, or infection, which may have affected fetal growth and development. Listed below are such microscopic findings. Of note, many of the hypoxic changes will be exaggerated in sections of the peripheral placenta due to naturally low blood flow at the margins; therefore, avoid the marginal placenta for your routine sections or clarify their location in your block description.

The presence of ***nucleated fetal red blood cells (nRBC)*** in the fetal and placental circulation at term is abnormal. nRBC have dark nuclei with smooth and sharp nuclear membranes and are appreciably smaller than mature red blood cells and lymphocytes. In term placentas, a ratio of nRBC to leukocytes over 2:3 is considered abnormal.

nRBC are believed to represent fetal compensation to hypoxia of durations from hours, days or weeks. Normally, nRBC are rarely seen in fetal vessels of the term placenta. Their numbers increase in response to hypoxia or asphyxia, seen more commonly with maternal diabetes mellitus, abruptio placentae, infection and fetal growth retardation. They are also seen in congenital cytomegalovirus infection and syphilis and rarely in cases of fetal triploidy, trisomy 13, trisomy 21, Rh incompatibility and lacerated fetal vessels.

Syncytiotrophoblastic knots are aggregates of small, closely packed and densely stained nuclei. They are uncommon before 32 weeks gestation; their numbers increase steadily until term, when 30% of villi have knots. Knots in more than 33% of villi are considered excessive (count 100 villi in a maternal zone section from the placental center) - keep in mind, the number of knots is also related to the thickness of the histologic section. A generalized increase in knots may be seen in postdates, pre-eclampsia, maternal diabetes mellitus and hypertension.

Tenney-Parker change refers to increased syncytial knots present earlier in gestation, which may be seen in pre-eclampsia secondary to reduced maternal blood flow through the intervillous space, a reflection of reduced oxygen availability.

Excessive number of cytotrophoblastic cells. Villous cytotrophoblastic cells form a complete mantle around immature villi and diminish with advancing pregnancy. Cytotrophoblastic cells are best demonstrated by PAS stain: cytoplasm of syncytiotrophoblast is PAS positive, cytoplasm of cytotrophoblast is PAS negative. In normal term placentas, cytotrophoblasts are seen in 20-40% of villi. A greater number may be seen in postdates, maternal diabetes mellitus, pre-eclampsia, hypertension, Rh incompatibility and in conditions of fetal hypoxia. The extent of cytotrophoblastic hyperplasia indicates the severity of ischemia in hypertension and pre-eclampsia.

Deficiency of vasculosyncytial membranes (VSM). VSM are specialized areas of gas transfer, uncommon until about 32 weeks gestation with subsequent rapid increase in number until term, when they are present in 20% of villi. Deficiency of VSM, in less than 5% of villi, may be seen in postdates, pre-eclampsia, Rh incompatibility and maternal diabetes mellitus; in Rh incompatibility and diabetes mellitus, VSM deficiency is related to delayed villous maturation. Of note, VSM are not easily seen in areas when capillaries are collapsed. With VSM deficiency, the incidence of fetal hypoxia and low birth weight are higher.

Trophoblastic basement membrane thickening, assessed by PAS stain, is found in 3% of villi in 30% of normal term and many postdates placentas. It is seen in a higher proportion of villi in pregnancies complicated by pre-eclampsia,

essential hypertension, maternal diabetes mellitus and Rh incompatibility. As a consequence of uteroplacental ischemia, fetal hypoxia may develop.

Villous vascularity: hypovascular and hypervascular (chorangiosis). Normal villi contain about 5 vascular channels. *Villous hypovascularity* is signified by small, undilated villous blood vessels, not a reduced number of blood vessels. It is seen in delayed maturation or is secondary to fetal stem vessel thrombosis.

Villous hypervascularity is signified by an increased number of vascular channels, not merely vascular congestion or dilation. It occurs in maternal diabetes mellitus, pre-eclampsia and Rh incompatibility. *Chorangiosis* is defined as 10 or more vascular channels seen in 10 or more low-power fields of viable placental tissue in three placental areas. Overall, chorangiosis is rare, seen in less than 5% of placentas. Although the actual cause of chorangiosis is unknown, some consider it to be the sequela of chronic placental hypoxia and chronic decreased fetal perfusion (from an excessively long umbilical cord, thrombosis of placental fetal surface vasculature or high altitude). Chorangiosis may be the placenta's attempt to supply more diffusion space, and is seen more often in association with neonatal morbidity (including cerebral palsy), congenital malformations and death.

Placental dysmaturity-Villous maturity refers to a histologic appearance distinctly different than expected for the given gestational age, an often difficult distinction influenced by maternal factors and tissue fixation and storage. Assessment of villous maturity is difficult on placentas less than 37 weeks gestation. At term, the villi are small, with dilated vessels, compressed stroma and syncytial knots. Immature villi are larger, with small undilated vessels, a relatively large amount of stroma and no syncytial knots. Small isolated groups of immature villi may be seen in 97% of term placentas, representing newly formed villi. *Delayed maturation or villi immature for gestational age* may be present with maternal diabetes mellitus, Rh incompatibility, syphilis and Down's syndrome. *Accelerated maturation or villi more mature for gestational age* may be present in pre-eclampsia as a compensatory mechanism to counter the effects of inadequate uteroplacental blood flow.

Villitis, inflammation of the placental parenchyma, results from hematogenous spread of maternal blood borne infection and contiguous spread from endometritis and occurs in 10% of "at-risk" placentas. In more than 95% of cases, the etiologic agent is not clinically or pathologically identified. When identified, most cases are due to viral infections, although bacterial sepsis, spirochete, fungal and protozoal sepsis can also infect the placenta. The fetus is at risk for hematogenous, transplacental infection by pathogens which are able to

survive within Hofbauer cells. The villi and intervillous space typically are affected first; the membranes may be affected but this is more characteristic of ascending infections. Villitis may be focal, multifocal or diffuse; exudative, chronic or granulomatous; and neutrophilic, lymphohistiocytic or plasmacytic. Hemosiderin deposition is common. Neutrophils within and surrounding villi signify ***acute villitis***, a finding strongly suggestive of maternal or fetal bacteremia. Perivillous or intravillous chronic inflammation signifies ***chronic villitis***, a finding suggestive of either nonbacterial infection ("specific" chronic villitis) or possible immunologic disorder ("non-specific," chronic villitis, ***villitis of unknown etiology (VUE)***). ***Granulomatous villitis*** is characterized by histiocytic multinucleated giant cells; it is "non-specific" but has been reported with herpes simplex virus, varicella, toxoplasmosis, tuberculosis, leprosy, Chagas' disease and blastomycosis. To detect with certainty more than 90% of focal villitis, it is necessary to examine four blocks of placental parenchyma. Villitis is present in 5-34% of examined placentas and is more often seen in patients of lower socioeconomic class. The most frequently identified organisms are the TORCH group (***T***oxoplasma, ***R***ubella, ***C***ytomegalovirus, ***H***erpes and ***O***ther), Treponema pallidum (syphilis), and Listeria. Less than 5% have positive cultures or corroborative evidence of fetal infection. VUE encompasses variable lesions, histopathologically indistinguishable from specific villitis, from occasional villous involvement to extreme involvement where all villi have some pathology. The prominent features of VUE are proliferative villitis, necrotizing villitis, granulomatous villitis, fetal vasculopathy, avascular villi, placental dysmaturity, increased nucleated red blood cells, hemosiderin, hemorrhagic vasculitis, necrotizing deciduitis, basal villitis, chorangiosis, and ischemia or infarcts. All or some of these abnormalities may be seen. The severity of villitis does not correlate with the severity of neonatal disease.

Chronic intervillositis, also called *massive chronic intervillositis (MCI)*, is a rare condition characterized by an inflammatory infiltrate of maternal mononuclear cells (histiocytes and lymphocytes) admixed with rare neutrophils in the intervillous space in the absence of villitis. There may be prominent intravillous and perivillous fibrinoid and vasculitis. MCI may be seen with maternal diabetes mellitus, pre-eclampsia, hypertension, drug use and systemic lupus erythematosus. It is highly associated with fetal growth retardation and fetal death, and may be a cause of recurrent abortion.