Placental Pathology, a Survival Guide

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GROSS PLACENTAL FINDINGS/EXAMINATION

I believe that all placentas should have at least a gross examination, saving the full histopathologic examination for a defined subset (Table 1). At the Massachusetts General Hospital, all placentas are delivered to the pathology department with a minimal required set of clinical information: maternal gravidity, parity, gestational age, and a blank section to provide any other information deemed pertinent by the obstetric staff. Using only these provided data, we triage the placenta into a "hold" or "examine" category. Hold placentas are those that do not meet criteria as described in Table 1 and are basically normal-term singleton livebirths who received prenatal care and delivered in the hospital without maternal or fetal/infant pathologic history or complications. The hold placentas are placed in a large, locked refrigerator for at least 7 days and are disposed of after 7 days so long as the infant is not transferred to the neonatal intensive care unit and the mother is not readmitted with an obstetric or other complication. Maternal admission and neonatal intensive care unit admission lists are checked daily for these events. The examine category includes all placentas from deliveries other than those described in Table 1 or are maternal readmissions or neonatal intensive care unit admissions.

Placentas are stereotypic organs that lend themselves to template gross description (Table 2), ensuring that all the important information is obtained and facilitating dictation and transcription. Deviations from this template-for example, twin gestation or other multiples or fragmented placentas-can be handled without the template or with minor deviations from it. The template ensures that the most critical information is noted: color, cord length[1-3] (standards in Figure 1), lesions, and trimmed weight.[1,3-7] The importance of these gross findings is listed in Table 3. This also allows for easy sampling, as once the gross template is complete the necessary sections needed for histology are neatly outlined. We take at least 2 sections of cord (proximal to the placenta and proximal to fetus), 1 membrane roll (including the membrane rupture site), and 3 full thickness sections of parenchyma, including chorionic plate vessels. All parenchymal lesions should be sampled (just a small representative section), and at least one "normal" representative section of parenchyma needs to be sampled.

These "chunks" of placenta, the membrane roll, and the cord sections are placed into a small specimen jar with 10% formalin and fixed for at least 4 hours. Very sick babies or mothers need pathologic interpretation promptly, and these specimens should be processed the same day as accessioned. Others can be

fixed overnight, or as convenient. We fix the remaining placental tissues as well and save it until the case is complete.

HISTOLOGIC FINDINGS

Remembering that the placenta is an organ with circulations from both the mother and the fetus, examination of the placenta should look for pathology from both individuals. Historically, the focus of placental histopathology has been on maternal side diseases/disorders. Recently, much attention has been focused on the fetal side. There may be much more importance in the fetal histopathology of the placenta in terms of predicting or explaining subsequent morbidity.

Maternal side diseases/disorders that affect the placenta are many and are too numerous to describe herein. Instead, I will focus on those that have been shown to have important fetal sequellae or recurrence risk.

Maternal Placental Perfusion Pathologies

The uterine vessels that perfuse the placenta can be damaged due to myriad diseases/disorders and lead to ischemia to the placenta, either regionally or globally. The resultant placental pathology is an infarct (villi collapsed upon each other with empty intervillous space-no maternal blood-and undergoing necrosis from the inside out-in early stages maintaining fetal blood flow). Regional under/absent perfusion results in a focal placental infarct, usually near the margin, and typically in a pyramidal shape with the base along the maternal floor (Figure 2, A). These infarcts are quite common at term or after term and are related to senescence. Preterm placental infarcts are less common. The significance of infarcts has to do with the placental reserve. Infarcts in normal-sized, well-developed placentas, even if large, are usually of no significance. Although placental infarcts are common, multiple infarcts or infarcts that make up more than 5% of the placental mass are considered pathologic and may impact the fetal oxygen/nutrient state. Small placentas or placentas damaged by other pathologies have less reserve, and therefore the fetus is more susceptible to injury due to any sized placental infarct. Global ischemia to the placenta from diffuse vascular damage has a different pathology. The infarcts tend to be small, multiple, and more "central" in the placental mass (in the "watershed" zone; Figure 2, B). These, in my experience, are much more characteristic of severe, chronic, uteroplacental vascular insuf- ficiency. In addition to infarcts, which are really absent maternal perfusion, there are other findings that correlate with chronic ischemia to the placenta. These have been well described in the literature8 and include small villi (usually containing only one capillary), large syncytial knots (containing more than 10 nuclei, often larger than the villous), and absence of midsized villi, giving the placental histology a look of only large and small villi with abundant open maternal space (Figure 2, C).

In my experience, placental pathology of ischemia differs from that of hypoxemia. Maternal hypoxemia, generally severe and due to cardiopulmonary disease but also seen in high-altitude pregnancies, does not produce the above described changes of ischemia, but rather placentas with a dramatic increase in the amount of villous vessels (chorangiosis,[9-13] usually more than 20 or so vessels in a villous; Figure 3, A) and the presence of easily identifiable erythrocyte precursors (normoblasts; Figure 3, B). I have also seen this in a lethal case of peripartum cardiomyopathy.

Other findings related to maternal-side vascular pathology include thrombophilias.[14] Inherited (eg, protein C or S deficiency, factor V Leiden, sickle cell disease) or acquired maternal thrombophilias (eg, antiphospholipid antibody, and see herein) can lead to markedly increased fibrin/fibrinoid deposition in the maternal or intervillous space (Figure 4, A). The result is the villi are trapped by the material and are "chocked," leading to necrosis. There are some pregnancy-specific disorders leading to increased inter/perivillous fibrin deposition, including maternal floor infarct[15-20] (MFI; Figure 4, B) and massive chronic intervillositis[21-24] (MCI; Figure 4, C). These disorders are idiopathic, have a high recurrence rate in future pregnancies, and are thought to be immune mediated, a sort of maternal host versus fetal allograft rejection reaction.

Maternal floor infarct is a poorly chosen name to a rare finding of a vast amount of the maternal floor effaced by a confluent and thick layer of fibrin/fibrinoid. This layer effectively inhibits maternal perfusion of the associated placenta, which then is perfused only by the "backflow" of adjacent noninvolved regions. MFI is often associated with fetal morbidity and mortality. It is one of the placental causes of an elevated maternal serum α-fetoprotein. MFI is reported to have a significant recurrence risk; therefore, I recommend reviewing previous obstetric pathologies and alerting the clinicians to the recurrence risk. If there is associated elevated maternal serum α-fetoprotein as well, this provides a handy tool for the clinicians to follow the next pregnancy.

Massive chronic intervillositis is a striking finding in which the maternal space is filled with CD68-positive histiocytes and an admixed or nodular increase in fibrin is seen. The lesion can occur at any gestational age, although it has been reported to be most common in the first trimester (a cause of chromosomally normal first-trimester abortion). It has reportedly the highest recurrence risk of all placental pathologies and arguably the most significant sequellae, fetal death. The lesion can occur consequetatively or be interrupted, without any medical intervention or change in paternity, with totally normal full-term live birth pregnancies. MCI can also be a placental cause of elevated maternal serum α-fetoprotein. The diagnosis is always most striking in late second or third trimester and can be quite subtle in the first trimester. When diagnosed in a later gestation placenta, all previous obstetric pathology should be reviewed for the possibility of a missed subtle diagnosis.

The fetal consequence of any of these maternal vascular pathologies depends on the reserve of the placenta and fetus but may include intrauterine growth restriction and fetal death in utero.

Fetal Perfusion Defects

The fetus perfuses the placenta through the umbilical arteries, and the blood flows through the chorionic plate vessels into the villi and returns to the fetus, oxygen and nutrient rich, through the umbilical vein. The villi are perfused internally by the fetus and externally by the mother. Fetal perfusion defects have a characteristic pathology unique from that of maternal vascular pathology. The intervillous space (maternal lakes) are patent, but the villi are empty of functioning vessels and fetal blood (Figure 5, A). The term fetal thrombotic vasculopathy (FTV)[25-28] is the generic term used for all fetal perfusion pathologies and includes those that are thromboembolic (eg, from a fetal or umbilical source as might be seen in fetal diffuse intravascular coagulopathy, partial or intermittent cord obstructions as in true umbilical knots or membranous vessels), due to heart failure (leading to fetal-side hypoxia and endothelial damage presenting as sloughed endothelium in the villi and fragmented fetal red blood cells, previously called hemorrhagic endovasculitis [HEV][29-34]; Figure 5, C), due to damage to any fetal vascular wall (meconium myonecrosis: see below, inflammatory migration through a vessel as associated with acute chorioamnionitis, or inflammatory damage in chronic villitis), or due to hematologic disturbances (as seen in the increased red cell mass in infants of diabetic mothers or in leukemias and leukemoid reactions, as in infants with trisomy 21).

Toxic damage to fetal vessels results from meconium myonecrosis.[35-37] A high concentration of meconium exposure over a prolonged time interval can be toxic to the myocytes of the vessels in the umbilical cord or chorionic plate. The meconium appears to stimulate a chemotaxis and the sequellae of that (as well as an apparently direct toxic effect to the smooth muscle of the vascular wall). The lesion consists of an apoptosis of the smooth muscle cells (Figure 5, B) with a spatial distribution: the closer the myocytes are to the amniotic fluid, the more damaging. This results in a flaccid vessel, which can collapse and interrupt blood flow to both the fetus and/or the placenta, often with disastrous consequences. It is a common finding I see in postdate deliveries of unexpected "bad babies" who later are given the diagnosis of "cerebral palsy." There are no prospective trials, so currently this finding is diagnosed as "meconium myonecrosis" with a note to the neonatologist/pediatrician and delivering personnel that this infant should be followed earlier and more often to ensure that neurodevelopment is evaluated to assess for delay and intervene if appropriate.

Hemorrhagic endovasculitis is a distinctive histopathologic finding of damage to the endothelium of the villous vessels, resulting in extravasation of the fetal red blood cells into the vessel wall (Figure 5, C).[38-44] Well-developed cases

phenocopy recanalization of occluded vessels. Although this finding is thought to be due to "slow flow" or heart failure on the fetal part, it is most commonly seen in stillbirths and is likely a sequellae of fetal death. In livebirths, we consider it an ominous finding, a near-miss stillbirth, and have most often seen it in cases of severe fetal heart failure due to structural anomalies or severe hypoxemia.

Fetal consequence of FTV is a function of the amount of the placental mass involved and the specific etiology leading to FTV. Some have noted that focal FTV generally has no clinical significance, whereas diffuse FTV, especially due to HEV, is associated with grave neurologic compromised, and I often consider these near-miss stillbirths.

When confronted with FTV in a case, I always review the differential diagnosis: look for anatomic, inflammatory, toxic, and neoplastic etiologies to explain the finding, and put that in the report. FTV is often a pathologic finding without an anatomically determined etiology, and should be noted as such.

There are at least 2 other findings that suggest vascular compromise on the fetal side. These include massive villous edema, which may compress the small villous vessels (Figure 5, D), and intravillous hemorrhage (rupture of the villous vessels and free blood in the villous stroma, a finding seen in acute abruptions or cord accidents; Figure 5, E).

Placental Findings Associated With Fetal Neurologic Compromise

There are many findings associated with neurocompromise in the neonate, either immediate or delayed, expected or unexpected, in the preterm, term, or postterm infant. They have been nicely reviewed, and those reviews should be read by all with an interest in placental pathology. 45,46 The common findings include vascular compromise. I will review the findings and suggest reporting methods to minimize familial terror and maximize pediatric observance.

Inflammatory cells migrate through the fetal vessels in response to chemoattractants, including infectious organisms and meconium. The umbilical cord (Figure 6, A) and chorionic plate vessels (Figure 6, B) are most often involved. The result is local destruction and/or injury to the endothelium and vascular wall, leading to a thrombogenic focus, loss of vascular patency, and release of cytokines and other factors systemically (to the placenta and fetus). Marked "vasculitis" from fetal sources has been associated with neurologic compromise, likely for these reasons (see below for a more extensive discussion).47

Good, controlled data are limited in this critical arena. Most studies are retrospective and uncontrolled. What are best defensible include massive/diffuse acute villous edema associated with cerebral palsy48,49 and marked chorionic plate vasculitis associated with other forms of neurologic compromise.35-37,46-

50 Some pretty good retrospective data suggest that FTV from meconium myonecrosis is also associated with severe neurologic delay.[35,51] In my practice, these features are diagnosed with caution and with an appropriate phone call or comment in the report. I also try to get the report to both the delivering clinician as well as to the neonatologist and/or pediatrician (to ensure that the infant is followed). I use the following note when I am most concerned about the findings (and I always call the clinicians):

Comment: These findings are diffuse and dramatic. In some studies, similar findings have been associated with sequellae (neurodevelopmental delay, seizures, etc).

Placental Pathologic Findings With Immediate Neonatal Care Implications

The fetal implications of placental examination involve the findings that: require immediate clinical intervention, suggest a newborn risk for disease, explain an in utero etiology of immediate neonatal compromise or fetal/neonatal death, time an insult in broad time windows (more important in legal questions), and may have implications in assigning risk for the development of adult chronic disease.

Immediately relevant diagnoses are rare in placental pathology but are significant. Anything hematogenously disseminated by a mother or fetus can be identified by placental histopathologic examination. These include infectious organisms delivered to the placenta during maternal sepsis or viremia, thromboemboli, and metastatic disease from maternal[52] or fetal sources.[53,54] The cellular makeup of the blood from a mother or baby can also show evidence of maternal disease (eg, sickle cell disease or trait) or fetal disease (eg, dyserythropoetic anemia,[55] α-thalassemia, [56] etc). Suggestions of fetal maldevelopment can be made based on placental pathologic findings (single umbilical artery and urinary tract anomalies, for example[57]). And some specific classes of diseases may first present in the placenta, particularly inborn errors of metabolism.[58,59]

Congenital infections include most commonly those "ascending" from cervicovaginal flora causing acute chorioamnionitis or, more rarely, "transplacental" from hematogenously spread maternal disease.[60,61] Acute chorioamnionitis (ACA; Figure 7, A) is a very common histopathologic finding of a neurtrophillic infiltrate in the placental membranes.[60,61] It is considered to be nearly always due to a microbial infection of the amniotic fluid. There are some specific single-organism infectious etiologies of ACA that are diagnosable from placental histopathology (Table 4). The sequellae of ACA includes preterm rupture of membranes, preterm delivery, and thus all the sequellae of prematurity. The less commonly associated fetal sepsis is difficult to predict[62]; the only histopathologic finding associated with fetal sepsis is the presence of umbilical cord "arteritis" (fetal exudate through the umbilical arteries into Wharton jelly). Although the significance of diagnosing ACA and umbilical arteritis is not to

be understated, the more serious finding related to ACA is the local vascular damage and systemic endothelial damage from fetal inflammatory cells.[47,63-65] Local damage to the fetal vessels in the placenta results in a thrombogenic focus and/or an incompetent vessel, as discussed above. Thrombi can form in these damaged vessels and remain attached to the vessel or can embolize downstream to the villi (resulting in a fetal side placental infarct) or via the umbilical vein back to the fetus, where the most likely sites of embolization will be cerebral or renal. The effects would be obvious: congenital embolic stroke or renal or other visceral infarcts. The placenta should always be examined as a source for thromboemboli in neonatally diagnosed visceral infarcts or embolic strokes. Other than causing a thrombogenic site, the fetal inflammatory infiltrate is very slow to chemotax, resulting in slow movement out of the vessel, stasis within the vessel wall and lumen, and premature release of cytoplasmic contents (lysozymes and cytokines), which exacerbate the local response and stimulate the systemic response. This can result in a fetal septiclike picture without true sepsis.

The other route of congenital infection is through the placenta from a maternal hematogenous source.[66,67] Although the placenta, via its trophoblastic barrier, provides a protective function from transmission of infectious organisms and toxins, it also is the permissive source of transplacental transfer of these as well. Many viral particles passively transfer across the trophoblastic barrier, and others are actively transported. All infectious placentitis are rare. The most common transplacental infection is cytomegalovirus (CMV),[67] which can cause congenital infection either from primary or recurrent disease,[67] with others including parvovirus, herpes simplex virus, hepatitis B and C, and treponema pallidum. In active infections, many placentas will have characteristic histopathology, but often the findings are subtle (as in parvovirus, where inclusion is only present in fetal red blood cells) or absent (hepatitis B and C). The classic lesion is chronic villitis (Figure 7, B), a maternal inflammation of the villous stroma, often with associated intervillositis.[68] Damage from chronic villitis is due to both the rare congenital infection as well as the stromal reaction/inflammation, which results in vascular compression, villous ischemia, and necrosis (avascular villi). Most chronic villitities are not infectious in etiology (only about 1% are) and are thought to be a maternal immune-regulated rejection of the fetal allograft (see below).[69,70]

Specific diseases that allow for survival of the fetus can often be diagnosed first by placental pathology. Most inborn errors of metabolism will present as foamy distention of the syncytial trophoblastic cytoplasm, a diagnosis that ensures rapid specific diagnosis and early intervention as well as family reproductive counseling (Figure 8, A).[58] Beckwidth-Weidemann syndrome, a genetic disease characterized by increased incidence of pediatric tumors as well as other findings, can be suspected based on placental examination, as they characteristically have placentomegaly with mesenchymal dysplasia (Figure 8, B).[71-74]

Placental metastases from fetal neoplasms are rare. Neuroblastoma, the most common solid malignant tumor of childhood, is the most common fetal malignancy that involves the placenta,54,75 followed by hepatoblastoma76,77 and leukemia.78 Not infrequently, the fetus shows hydrops fetalis, and for that reason congenital malignancies should be added to the list of differential diagnoses of nonimmunologic hydrops fetalis. On gross examination, these tumors are frequently associated with an enlarged placenta (usually >1000 g) that is edematous and pale without visible nodules and resembles the gross appearance of erythroblastosis fetalis. On microscopic examination, the malignant tumor cells are frequently confined to the fetal circulation and rarely extend to the parenchyma of the chorionic villi in cases of neuroblastoma and hepatoblastoma; however, in cases of placental involvement by leukemia, there is typically diffuse infiltration of the chorionic villi by malignant fetal cells. This histologic finding is frequently associated with prominent hydropic change of the chorionic villi. Fetal primitive malignant tumors involving the placenta may be confused with intravascular hematopoiesis. Of note, this entity is not associated with an enlarged placenta, and it is typically seen in chorionic villi in abortions obtained from the 5 to 11 weeks' gestation.79 Finally, in contrast to maternal metastases, there are only very rare maternal consequences related to fetal malignancies. 80

Placental Pathology With Maternal Care Implications

Placental pathology can offer information regarding maternal health and the risk for future pregnancy complications. Much interest in the maternal side of the placenta has related to the effects of maternal disease on placental function. For example, the effects of hypertensive diseases (whether pregnancy related or not) on placental function and pathology have been discussed above. We can use these findings in nonhypertensive pregnancies to suggest ischemia related to other etiologies, that is, tobacco use, maternal sickle cell disease or trait, uterine anomalies like bicornuate uterus, etc.

Maternal infectious diseases are usually diagnosed before the placental pathology report returns, but some cases, especially congenital CMV, suggest further maternal testing. Congenital CMV severe enough to result in neonatal disease or intrauterine fetal death (IUFD) is rare and related to viral load. In most cases, the infection is the first for the mother, resulting in high viral load and transfer to the fetus through the placenta, resulting in fetal death. In other cases, recurrent CMV or CMV placentitis presenting in an older mother and resulting in fetal mortality may be enough to suspect maternal immunodeficiency and is an indication to evaluate for maternal HIV status.81

Syphilis82 and herpes simplex virus (genital or oral)83-85 often are clinically silent in pregnancy and evidenced only postpartum with neonatal sepsis or IUFD. Most other infections will present antenatal with some maternal symptoms.

Maternal malignant diseases can metastasize to the placenta or originate in the placenta, and they certainly carry significant maternal risk. Although the most common malignancies that present during pregnancy include those common in the reproductive age, metastases are typically hematogenous and occur early during pregnancy. Melanoma represents 8% of cancers in pregnancy, but it accounts for 31% of all placental metastases.[86] Leukemia and lymphoma (15%), followed by breast (13%) and lung (11%) carcinomas, sarcomas (8%), gastric carcinoma (3%), and gynecologic cancers (3%) are the other most common maternal malignancies that have been reported to involve the placenta.[52,87-94] On gross examination, the placenta may be enlarged or the lesions may be noted as dark brown areas simulating an infarction in up to 50% of cases.[95,96] On microscopic examination, the neoplastic infiltrate typically occupies the intervillous space, a component of the maternal vascular system, but in some instances villous or even fetal vascular invasion may be present, although extremely rare. The extent of placental involvement does not correlate with the incidence of fetal metastases, and in most instances there is placental metastases without fetal involvement[89,97]; however, the finding of fetal involvement is almost lethal for the fetus or newborn. It is also important to remember that there are primary lesions of the placenta that may be confused with metastatic deposits of maternal origin. These include placental melanocytic deposits seen in babies with congenital melanocytic nevi that can be confused with metastatic melanoma,[98,99] and adrenocortical or hepatic nodules that may occur within the placental tissue and may mimic more commonly metastatic carcinoma.[100-102] Finally, maternal malignant tumor metastatic to the placenta is indicative of stage IV disease for the mother and carries a very poor prognosis. As a rule, it is recommended to examine all placentas in cases in which a malignancy is known in the mother.

There are findings that may lead to clinical intervention or counseling in or before future pregnancies. These are the findings that are believed to be due to an abnormal immune response maternally "rejecting" the placental/fetal allograft. Although the specific etiology of these placental findings is unknown, their well-documented recurrence risk suggests they are immune based. The diagnoses probably represent a single class of disorders that have been subdivided pathologically and include those discussed above: maternal floor infarct,[16-18,20,103,104] villitis of unclear etiology,[105] massive chronic intervillositis/massive intervillous fibrin deposition.[21-24,106] The recurrence risk varies from 33% to 80% but is just an estimate, as no good denominator exists for the cases. Although no specific therapy is accepted for these cases, clinical intervention has included antithrombotic therapy, systemic steroids, as well as counseling about alternatives for reproduction.

Placental Findings With Legal Implications

We live in a litigious society with unreasonable expectations for pregnancy outcome. The unexpected "bad" outcome is filled with anger and guilt from the

family and from the clinician. The pathologist can offer the best intervention, with a clearly presented, unbiased report that can offer insight into the timing of the insult, most often clearing the clinician from liability and helping the family with understanding and grieving. In cases of unexpected complications associated with a livebirth, placental examination is critical. Timely interpretation and, hopefully, meeting with the family, neonatologist, obstetricians or other delivering personnel, nurses, and others involved in the care can be instrumental in obviating the need for legal interference. I truly believe that this it a duty of the pathologist at least to offer to have these meetings. The same holds for the unexpected stillbirth, in which, hopefully, the placental and autopsy findings can be discussed.

Most litigious claims deal with a critical period where intervention, if obtained, would have led to a "normal" outcome. In my practice, both in hospital and legal expert witness cases, the in-labor catastrophes are rare and, when present, are rarely either diagnosable or intervenable by the clinicians. Most cases of unexpected bad outcomes have chronic insults to the placenta. Most of the findings have been described above. The findings and their relative timings in relationship to delivery are presented in Table 5.

SUMMARY AND CONCLUSIONS

The placenta is a valuable tool to understand in utero events, predict neonatal outcome, help with reproductive choices, and prevent frivolous lawsuits. Placental pathologists are useful consultants to both obstetric and pediatric practices. Examination of the placenta is indicated in a defined subset of all deliveries.

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