OBSTETRICS

Classification of placental lesions

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Placental pathology can be useful in a variety of ways including immediate diagnosis of important conditions affecting the mother or infant, identifying conditions that are likely to recur in subsequent pregnancies, separating clinical syndromes into distinct pathological phenotypes for further investigation, and uncovering the underlying cause of unexpected adverse outcomes. Classification of placental lesions has evolved from being a purely descriptive exercise through a stage in which the major pathophysiological processes such as disorders of maternal implantation and the amniotic fluid infection syndrome were first described to a recently proposed comprehensive classification system that includes all of the major maternal and fetal vascular and infectious and idiopathic/immune inflammatory processes (Amsterdam Placental Workshop Group). Implementation of this unified system with reproducible grading and staging should help establish evidence-based recommendations for placental submission and facilitate progress in studying the pathogenesis, diagnosis, and treatment of obstetric disorders with an underlying placental etiology.

Key words: abruption, adverse pregnancy outcome, chorioamnionitis, clinical implications, delayed villous maturation, fetal vascular, maternal vascular, placenta, placental pathology, recurrent lesion, underperfusion, vascular lesions of the placenta, villitis

The placenta is the perennial Holy Grail, a putative diary of intrauterine life promising to explain the mysteries underlying poor pregnancy outcome. Its practical counterpart, placental pathology, is finally emerging as a respectable specialty after many years of confusion related to experts with divergent views, pathologists with varying levels of interest and relevant training, and nomenclature having little relationship to either the underlying biology or clinical presentation.

Recent progress has been realized through the gradual acceptance of a standardized, reproducible, and biologically based classification system. Much work remains to disseminate this new information to practicing pathologists and clinicians.

In this review, I will summarize the utility of placental diagnoses, review early contributions to our understanding of placental pathology, go into more depth describing the new Amsterdam international consensus criteria for placental diagnosis (Table 1), and conclude by speculating on how further progress in this area could facilitate the goals of the Human Placental Project to develop biomarkers and imaging techniques that can identify placental disease processes in real time when targeted intervention may be of benefit.[1,2]

Utility of placental examination

Submission of placentas for examination generally follows 1997 College of American Pathologists guidelines.[3] Approximately 40-50% of all placentas delivered in a high-risk setting will be examined according to these criteria.[4,5]

Additional high-quality evidence is needed to decide whether these guidelines are optimal for patient care. Useful information from a competently performed placental evaluation falls into the following 4 categories: (1) identification of previously unsuspected disease processes in the mother or infant that require immediate attention (eg, fragmentation suggestive of retained placenta or placenta accreta, unusual infections such as cytomegalovirus or listeria, and findings suggestive of aneuploidy or metabolic storage diseases); (2) conditions associated with a high probability of recurrence in subsequent pregnancies (Table 2); (3) information that can guide the management of future pregnancies or influence the long-term care of mother and infant (Table 3); and (4) diagnoses that provide a specific explanation for an adverse outcome such as fetal death, fetal growth restriction (FGR), spontaneous preterm birth, or central nervous system (CNS) injury.

These outcomes all have a wide differential diagnosis that placental pathology can sort through for the purposes of quality assurance, risk management, and patient education (Table 4). Although these benefits are important, a more thorough understanding of placental abnormalities could both expand and focus the utility of placental examination.

Background

Placental pathology in its earliest stages focused on macroscopic abnormalities such as battledore placentas, succenturiate lobes, and velamentous insertions of the umbilical cord (UC). Although distinctive, these conditions proved not to be closely related to adverse outcomes. A series of seminal studies published between 1970 and 1995 laid the groundwork for our present understanding of placental pathology. Pijnenborg et al[6] established the conceptual framework for disorders of placental implantation and their sequelae. Blanc[7] first delineated the sequence of placental changes that characterize amniotic fluid infection. Harris[8] distinguished marginal venous abruption

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Received May 4, 2015; revised May 15, 2015; accepted May 26, 2015.

The author reports no conflict of interest.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.05.056

TABLE 1
Placental classification (incorporating the 2014 Amsterdam Placental Workshop Group criteria)

1. Placental vascular processes
   a. Maternal stromal-vascular lesions
      - Developmental
        - Superficial implantation/decidual arteriopathy
        - Increased immature extravillous trophoblast
      - Malperfusion
        - Global/partial
          - Early: distal villous hypoplasia
          - Late: accelerated villous maturation
        - Segmental/complete
          - Villous infarct(s)
      - Loss of integrity
        - Abruptio placenta (arterial)
        - Marginal abruption (venous)
          - Acute
          - Chronic
   b. Fetal stromal-vascular lesions
      - Developmental
        - Villous capillary lesions
        - Delayed villous maturation (maturation defect)
        - Dysmorphic villi
      - Malperfusion
        - Global/partial
          - Obstructive lesions of umbilical cord
          - Recent intramural fibrin in large fetoplacental vessels
          - Small foci of avascular or karyorhectic villi
        - Segmental/complete
          - Chorionic plate or stem villous thrombi
          - Large foci of avascular or karyorhectic villi
      - Loss of integrity
        - Large vessel rupture (fetal hemorrhage)
        - Small vessel rupture (fetomaternal hemorrhage)
        - Villous edema
2. Placental inflammatory-immune processes
   a. Infectious inflammatory lesions
      - Acute
        - Maternal inflammatory response: chorioamnionitis, subchorionitis
        - Fetal inflammatory response: chorionic/umbilical vasculitis
      - Chronic
        - Villitis (CMV, others)
        - Intervillositis (malaria, others)
   b. Immune/idiopathic inflammatory lesions
      - Villitis of unknown etiology and related/associated lesions
        - Chronic villitis
        - Chronic chorioamnionitis
        - Lymphoplasmacytic deciduitis
        - Eosinophil T-cell fetal vasculitis
      - Chronic histiocytic intervillositis
3. Other placental processes
   - Massive perivillous fibrin(oid) deposition (maternal floor infarction)
   - Abnormal placental shape or umbilical insertion site
   - Morbidly adherent placentas (accreta)
   - Meconium-associated changes
   - Increased circulating nucleated red blood cells

CMV, cytomegalovirus.

Redline. Classification of placental lesions. Am J Obstet Gynecol 2015.

from the much less common syndrome of arterial rupture and abruptio placenta. Benirschke and colleagues[9,10] described how early marginal venous abruptions could progress to the chronic abruption-oligohydramnios sequence and was the first to describe the important lesion known as maternal floor infarction. Stallmach et al[11] demonstrated the association between delayed villous maturation (maturation defect) and fetal death. Altshuler and Russell[12] brought idiopathic chronic villitis to attention, and Altshuler[13] was the first to describe villous chorangiosis. Finally, Sander[14] described the patterns that would later come to be known as fetal thrombotic vasculopathy (now segmental fetal vascular malperfusion).

A more systematic approach to placental diagnosis was undertaken by the Perinatal Section of the Society of Pediatric Pathology beginning in 1998.[15-17] Ensuing publications proposed and validated the grading and staging of lesions related to amniotic fluid infection and the maternal and fetal vascular disorders. Building on this work, a schematic framework for all placental lesions was presented at the International Federation of Placenta Associations meeting in 2006.[18] These efforts provided the background for a comprehensive system proposed by 26 placental pathologists from around the world who met in Amsterdam in September 2014.[1] The consensus recommendations agreed upon during this meeting and in subsequent online discussions are incorporated into the next section and have been submitted for publication.

A secondary goal of the meeting was to establish sampling guidelines for placental evaluation. Although not the focus of this review, the following recommendations were made: submit 4 blocks as a minimum; one to include 2 cross-sections of the UC and a roll of the extraplacental membranes including part of the marginal parenchyma; 3 others containing full-thickness sections of normal-appearing placenta parenchyma taken from within the central two thirds of the disc including one adjacent to the UC insertion site.

The proposed new framework for placental classification (Table 1) is discussed in the following text.

Placental vascular processes

The placenta is essentially an interhemal membrane mediating the exchange of

nutrients and waste products between the maternal and fetal circulations. It is therefore not surprising that abnormalities in the structure and function of these circulatory beds are dominant patterns of placental injury.

Maternal stromal-vascular lesions

Developmental abnormalities of the maternal stromal-vascular compartment of the placenta have recently been reviewed and contribute to placental dysfunction via malperfusion and loss of integrity (discussed below).[19] For the purposes of this review, I will say only that developmental abnormalities all appear to involve defects in the appropriate differentiation and expansion of trophoblast, both extravillous (shallow implantation, lack of spiral artery remodeling, increased trophoblast islands and cysts in the intervillous space) and villous (persistent cytotrophoblast). Although some of these defects may be intrinsic to the trophoblast, most evidence suggests that they are caused by poorly understood maternal genetic or environmental factors that shape the early intrauterine environment.

Maternal vascular malperfusion develops as a consequence of abnormal spiral artery flow and can be separated into 2 subgroups.[16] The first, global/partial maternal vascular malperfusion, leads to accelerated villous maturation (Figure, A). Accelerated maturation is the term agreed upon to encompass all of the histological changes seen in portions of the villous tree deprived of the low-velocity, high-volume maternal blood flow that characterizes normal placentas.

These findings include alternating areas of agglutinated villi with increased syncytial knots and intervillous fibrin and villous paucity due to decreased villous branching. When paucity affects more than 30% of all distal villi, the process is termed distal villous hypoplasia. The second pattern, segmental/complete maternal vascular malperfusion, is characterized by villous infarcts which represent areas of ischemic necrosis overlying occluded spiral arteries. Whereas single infarcts, especially at the placental margin, are not unusual in term placentas, any infarct in a preterm placenta should be considered abnormal.

Loss of maternal vascular integrity encompasses 2 distinct processes. The first, abruptio placenta, frequently occurs secondary to arterial maldevelopment in preeclampsia and represents the rupture of incompletely remodeled spiral arteries due to ischemia-reperfusion or atherosis. Vasoactive drugs (cocaine or nicotine) and shear stress (trauma or uterine rupture) can also cause arterial hemorrhages. Abruptio placenta is characterized by central location and placental evidence of high pressure flow (large volume, indentaton of the basal plate, and extension into the intervillous space). Although most cases lead to immediate delivery, some arterial hemorrhages evolve gradually, leading to overlying recent villous infarction (subacute abruptio placenta).

TABLE 2
Placental lesions with significant recurrence risk in subsequent pregnancies

Rare
Chronic histiocytic intervillositis (75–90%)[53]
Massive perivillous fibrin(oid) deposition (maternal floor infarction) (40–60%)[64]
More common
Villitis of unknown etiology (25–50%)[46]
Placenta accreta (25–30%)[65]
Severe global/partial maternal malperfusion (10–25%)[66]
Spontaneous preterm birth with histological chorioamnionitis (10–25%)[67]

Redline. Classification of placental lesions. Am J Obstet Gynecol 2015.

TABLE 3
Management implications of current placental diagnoses: selected examples

Severe global/partial maternal vascular malperfusion
Evaluate maternal cardiovascular status, glucose tolerance, thrombophilia, and renal function; suggest weight loss; consider ASA therapy, uterine artery Doppler, early third-trimester placental ultrasound, early delivery in subsequent pregnancies
Spontaneous preterm delivery with histological chorioamnionitis
Extend neonatal antibiotics, treat underlying periodontal disease or chronic endometritis, early second-trimester cervical ultrasound, cerclage
Idiopathic/immune lesions (chronic villitis [VUE]), massive perivillous fibrin(oid) deposition ([maternal floor infarction] chronic histiocytic intervillositis)
Genetic counseling; maternal autoimmune testing; weight loss; consider low-molecular-weight heparin, aspirin, and/or immunosuppressive therapy; intensive early pregnancy surveillance; elective early delivery
Complete/segmental fetal vascular malperfusion with neonatal sequelae
Maternal/neonatal thrombophilia workup, diabetes screen, maternal platelet evaluation
Delayed villous maturation
Diabetes screen, suggest weight loss, perform third-trimester fetal movement counts, consider delivery prior to 40 weeks

ASA, aspirin; *VUE*, villitis of unknown etiology.

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TABLE 4
Common underlying placental causes of specific adverse outcomes

Preterm fetal death	
	Global/partial maternal vascular malperfusion (accelerated maturation), global/partial fetal vascular malperfusion (UC accident), abruptio placenta
Spontaneous preterm birth	
	Acute chorioamnionitis, marginal abruption, mild global/partial maternal malperfusion (accelerated maturation)
Fetal growth restriction/indicated preterm birth	
	Global/partial maternal malperfusion (accelerated maturation), chronic villitis (VUE), complete/segmental fetal vascular malperfusion (fetal thrombotic vasculopathy), fetal stromal-vascular developmental lesions
Term fetal death	
	Abruptio placenta, global/partial fetal vascular malperfusion (UC accident), fetomaternal hemorrhage, delayed villous maturation
CNS injury at term	
	Complete/segmental fetal vascular malperfusion (fetal thrombotic vasculopathy), global/partial fetal vascular malperfusion (UC accident), chronic villitis (VUE) with obliterative fetal vasculopathy, acute chorioamnionitis with severe fetal cellular inflammatory response, multiple placental lesions

UC, umbilical cord; *VUE*, villitis of unknown etiology.

Redline. Classification of placental lesions. Am J Obstet Gynecol 2015.

The second process, marginal abruption, represents the rupture of maternal veins, usually at the periphery of the placenta.[8] Risk factors include sudden changes in uterine geometry (rupture of membranes, cervical insufficiency), poor support (lower uterine segment implantation, abnormal marginal anatomy), increased maternal venous pressure, and decidual inflammation (chorioamnionitis).

Acute marginal abruption is an important cause of spontaneous preterm birth but only rarely causes fetal hypoxia. Chronic (marginal) abruption develops when acute marginal abruption does not progress to delivery. The hallmarks of chronic abruption include circumvallate membrane insertion, organizing marginal blood clots, and hemosiderin deposition. Severe cases show diffuse chorioamnionic hemosiderosis, reflecting hemorrhage into the amniotic fluid.[20]

Fetal stromal-vascular lesions

Developmental abnormalities of the fetal stromal-vascular compartment of the placenta can be separated into 3 categories.

Delayed villous maturation (also known as distal villous immaturity or maturation defect) is characterized by a decreased fetoplacental weight ratio, excessive villous stroma, and central capillaries lacking vasculosyncytial membranes (Figure, B).[21] This pattern is seen with diabetes, some cases of FGR, and chronic umbilical cord obstruction.[22] Lack of placental reserve in these placentas may increase the risk of fetal death.[11]

Villous capillary lesions include chorangiosis (hypercapillarization of terminal villi), chorangioma (a benign placental vascular tumor arising in stem villi), and multifocal chorangiomatosis (a more pervasive developmental abnormality involving small vessels at the periphery of immature intermediate villi).[23,24] Although distinct, all share a relationship with maternal hypoxemia and/or excessive fetal growth factor expression. They sometimes occur together in conditions such as Beckwith Wiedemann syndrome.[25]

Dysmorphic villi represent a more pervasive disorder encompassing abnormalities in villous architecture that resemble features seen in aneuploid gestations. These include irregular contour, trophoblast inclusions, cystic degeneration, stromal overgrowth, proximal-distal villous disproportion, and abnormal vascular patterning.[26,27] Mesenchymal dysplasia is the most dramatic example of this pattern.[28] Some cases of dysmorphic villi may represent examples of confined placental mosaicism.[29]

Fetal vascular malperfusion can be separated into 2 subgroups.[30] Global/partial, often associated with potentially obstructive umbilical cord lesions such as hypercoiling, stricture, abnormal placental insertion site, or long-standing fetal entanglements, is characterized by histological features suggestive of increased venous pressure (dilatation or mural fibrin deposition in large fetoplacental veins; Figure, C) and poor circulation in the most distal portions of the villous tree (scattered small foci of avascular villi; Figure, D). Its clinical correlate, chronic partial/ intermittent umbilical cord obstruction, has been associated with CNS injury.[31,32]

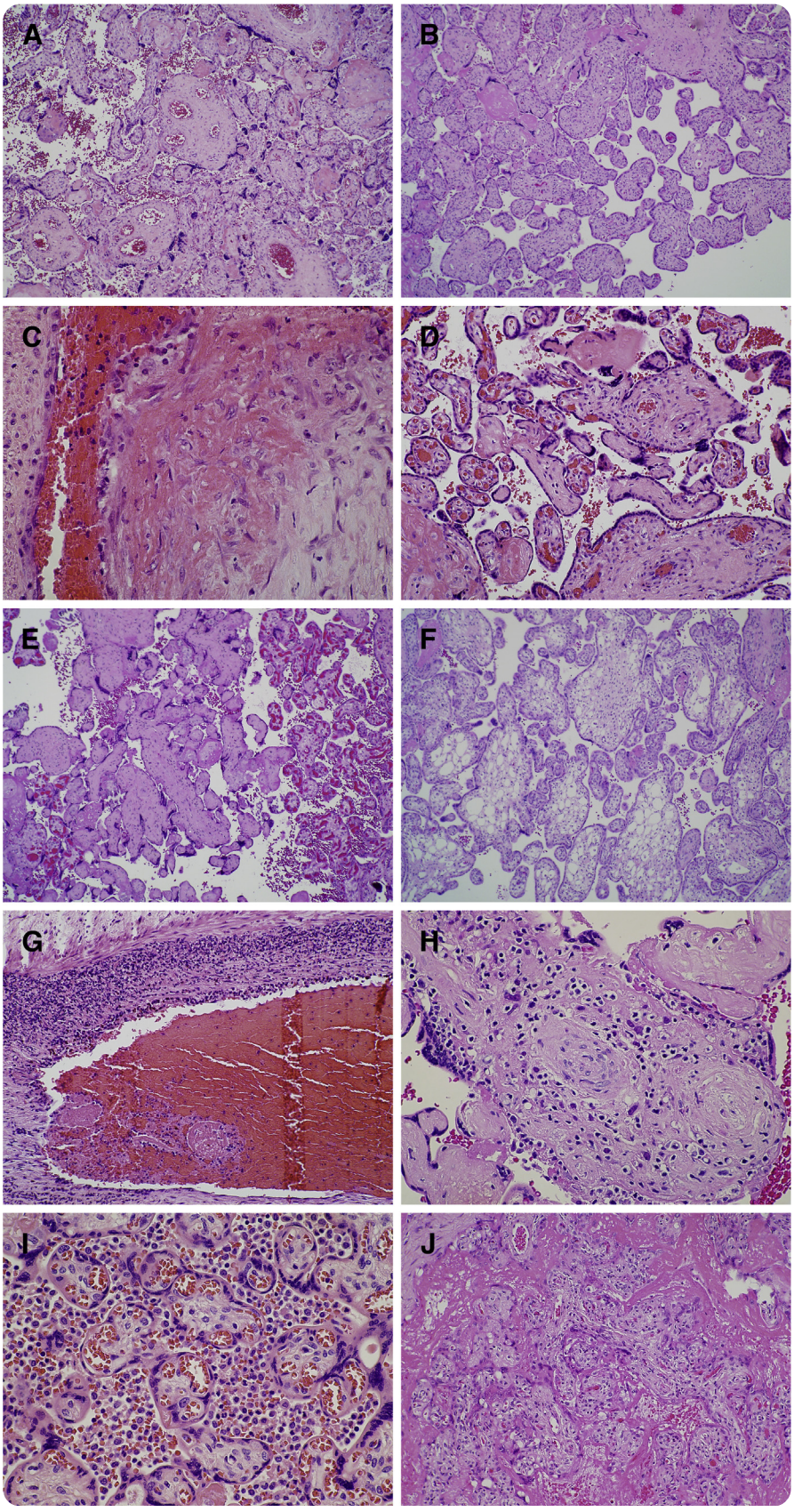
The second pattern, segmental/complete occlusion of large fetoplacental vessels by thrombi, leads to larger foci of degenerating downstream villi.[33,34] These villi initially show degenerative changes (stromal-vascular karyorrhexis) and eventually lose all vessels (avascular villi) (Figure, E). When extensive, this pattern has been called fetal thrombotic vasculopathy and has been associated with CNS injury and other adverse outcomes.

Loss of fetal vascular integrity encompasses 2 processes: hemorrhage and edema. Fetal hemorrhages can involve large vessels (eg, ruptured vasa previa) or smaller vessels in the distal villi (fetomaternal hemorrhage). The latter can present as intervillous thrombi.[35,36] Significant amounts of fetomaternal hemorrhage may be associated with increased fetal nucleated red blood cells (NRBC) in the placenta and a positive maternal Kleihauer Betke test. Edema of the placental villi accompanies hydrops fetalis, and placental pathology can contribute to differential diagnosis by highlighting coexisting fetal anemia

(increased NRBC) or identifying a specific etiology (eg, parvovirus inclusions).

A second pattern of edema seen in the immature intermediate villi of very premature placentas has been associated with perinatal death, CNS injury, and long-term neurodevelopmental disability (Figure, F).[37-39] A recent study suggests that a third pattern, patchy nonspecific edema of distal villi, is correlated with severe fetal acidemia in term infants.[40]

FIGURE
Clinically significant placental lesions



A, Accelerated villous maturation: clusters of agglutinated distal villi with increased syncytial knots and intervillous fibrin alternate with areas of villous paucity (magnification, ×10). **B,** Delayed villous maturation: distal villi show excessive stroma, central capillaries, and decreased vasculosyncytial membranes (magnification, ×10). **C,** Global/partial fetal vascular malperfusion (1): recent intramural fibrin is seen below the endothelium in a large fetoplacental vessel (magnification, ×40). **D,** Global/partial fetal vascular malperfusion (2): a small cluster of distal villi lacking fetal vessels (avascular villi) is surrounded by normal villi (magnification, ×20). **E,** Complete/segmental fetal vascular malperfusion: a large branching tree of proximal and distal villi lacking fetal vessels (avascular villi) is flanked by normal villi (magnification, ×10). **F,** Villous edema: proximal villi are expanded by excessive extracellular fluid (magnification, ×10). **G,** Acute chorioamnionitis with severe fetal cellular inflammatory response: confluent neutrophils with associated endothelial damage distort the upper (amniotic fluid facing) wall of a large chorionic plate vessel (magnification, ×20). **H,** Chronic villitis with obliterative fetal vasculopathy: proximal villus with stromal lymphocytes, obliteration of fetal arteriolar lumen, and a few surrounding avascular villi (magnification, ×40). **I,** Chronic histiocytic intervillositis: monocyte-macrophages (histiocytes) fill the intervillous space surrounding distal villi (magnification, ×40). **J,** Massive perivillous fibrin(oid) deposition (maternal floor infarction): fibrin and fibrinoid extracellular matrix fills the intervillous space surrounding distal villi (magnification, ×20).

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Placental inflammatory-immune processes

The placenta resides at 2 important interfaces: with the outside environment (cervicovaginal canal) and between antigenically distinct organisms (mother and fetus). An incompletely resolved tension exists between the need to promote local immune responses to protect against exogenous microorganisms and to suppress them to prevent fetal rejection. This results in increased susceptibility to infection, occasional breakdown in tolerance leading to immune mediated allograft-type responses, and helps explain why cellular inflammation is the major nonvascular abnormality observed in the placenta.

Infectious inflammatory lesions

Acute cellular inflammatory responses to ascending amniotic fluid infections by bacteria and fungi involve 2 separate immune systems: (1) maternal, with neutrophils entering chorioamnion via decidual venules in the membranes and the chorionic plate from the intervillous space (acute chorioamnionitis) and (2) fetal, with neutrophils entering the chorionic plate and Wharton's jelly by migrating through the walls of large chorionic and umbilical vessels (fetal and/or umbilical vasculitis).

The progression of each response is stereotypical and can also be graded for severity.[7,15] The maternal cellular inflammatory response begins in the subchorionic fibrin and at membranous choriodecidual interface (stage 1), spreads to the fibrous chorion and amnion (stage 2), and eventually leads to necrosis of the amnionic epithelium (stage 3). The Amsterdam criteria recognize only stages 2−3 to represent a fully developed histological chorioamnionitis, with stage 1 being a sensitive but less specific early indicator of evolving amniotic fluid infection.

Fetal cellular inflammation is first observed in the chorionic vessels and umbilical vein (stage 1), progresses to involve umbilical arteries (stage 2), and finally enters the umbilical cord stroma (stage 3). Fetal morbidity with chorioamnionitis is more commonly related to elevated circulating cytokines than fetal infection, and arteritis (fetal stage 2) is associated with higher levels of cytokines than phlebitis alone.[41,42] Confluent inflammation (fetal grade 2) and the presence of thrombi in acutely inflamed chorionic vessels are other important adverse prognostic features (Figure, G).[38,43]

Chronic cellular inflammatory responses to hematogenous infection by viruses and protozoa are usually confined to the villous stroma and intervillous space.[12] Common TORCH (toxoplasmosis, other [hepatitis B], rubella [German measles], cytomegalovirus, and herpes simplex virus)-type organisms such as cytomegalovirus cause a diffuse villitis with edema, fibrosis, and plasma cells. Less common infections, such as malaria, are associated with inflammation that surrounds but does not involve the villi (chronic intervillositis).[44] A few infections such as listeriosis can cause all 3 patterns, chorioamnionitis, villitis, and intervillositis, in the same placenta.[45] Unlike ascending infection, morbidity and mortality with hematogenous infection is more strongly correlated with fetal infection than elevated cytokines or the extent of placental damage.

Immune/idiopathic inflammatory lesions

Villitis of unknown etiology (VUE) is a T-cell−mediated disorder targeting the distal villous tree and characterized by chronic cellular inflammation of villous stroma (villitis) and, in some cases, the intervillous space (intervillositis and perivillous fibrin deposition) and stem villous vessels (obliterative fetal vasculopathy) (Figure, G).

Based on numerous studies over a 20 year period, VUE is now thought to be a maternal graft vs host−type response to fetal antigens in the placenta.[46,47] High-grade VUE (extensive or associated with obliterative fetal vasculopathy) has been associated with FGR, CNS injury, and fetal death. Additional important aspects of VUE include its high prevalence (approximately 5-10% of term placentas), increased incidence and severity in obese patients, and significant recurrence risk (25-50%).[48-50]

Other chronic inflammatory processes that are more common in the presence of VUE include chronic chorioamnionitis, lymphoplasmacytic deciduitis, and eosinophilic T-cell fetal vasculitis.[51,52] All can also occur independently. It has been suggested that chronic chorioamnionitis may be an underappreciated cause of spontaneous preterm birth.

Chronic histiocytic intervillositis is a rare idiopathic inflammatory lesion distinct from VUE and associated lesions.[53] It is characterized by a monomorphic maternal histiocytic infiltrate in the intervillous space without accompanying VUE (Figure, G). Occasionally this disorder overlaps with maternal floor infarction (described in the following text). Like maternal floor infarction, chronic histiocytic intervillositis is strongly associated with miscarriage, FGR, indicated preterm birth, and early intrauterine fetal demise. It has the highest recurrence rate of any placental lesion, sometimes affecting 10 or more consecutive pregnancies. Limited evidence suggests that affected patients may respond to aspirin, heparin, or immunosuppressive therapies.[54]

Other pathological processes

Placental lesions that do not fit comfortably into either the vascular or inflammatory categories include abnormalities of placental shape, morbidly adherent placentas (accreta), increased circulating NRBC, and the effects of prolonged meconium exposure.[55-57] Because of limited space, these will not be discussed further in this review.

One additional lesion of uncertain pathogenesis deserves comment because of its frequent underdiagnosis, strong association with adverse outcomes, and high recurrence rate: massive perivillous fibrin(oid) deposition, commonly known as maternal floor infarction, characterized by large amounts of fibrin and fibrinoid matrix surrounding a significant proportion of the distal villous tree (at least 30%) (Figure, H). This process can present at any gestational age and is strongly associated with recurrent miscarriage, severe FGR, early fetal death, spontaneous and indicated

preterm birth, and CNS injury.[58,59] Its pathogenesis remains obscure, but anecdotal evidence suggests that it may represent a reaction to diffuse trophoblast damage secondary to a variety of stressors including autoimmune disease, maternal thrombophilia, gestational hypertension, fetal long-chain 3-hydroxyacyl-CoA dehydrogenase mutations, and Coxsackie virus A16 infection.[60-63] A pathology report with this diagnosis should never be ignored.

Future directions

A simple, comprehensive, and widely accepted classification system is a prerequisite for the definition of robust and reproducible placental phenotypes. Defining the clinical relevance of each phenotype still requires additional study to more precisely establish the relative importance of severity (grade), duration (stage), extent of involvement, and different combinations of placental lesions. Once clinical context and significance are better understood, it should be possible to refine submission guidelines and decrease the number of unhelpful placental examinations, thereby reducing costs to the health care system.

The establishment of robust phenotypes is also critical for the interpretation of new genetic and epigenetic data, delineation of mechanistic pathways, and understanding the effects of exogenous environmental exposures on placental function. The goals of the recently initiated Human Placenta Project, to develop new biomarkers and imaging techniques allowing prospective diagnosis and the development of novel targeted therapies, are unlikely to be realized if pathological phenotype and data from the various "omics" technologies are not considered together.

Even in a hypothetical future scenario in which these exciting new diagnostic and therapeutic modalities are realized, placental pathology will likely continue to play an important role, serving as a gold standard for diagnosis, quality assessment, diagnostic test evaluation, and comparative effectiveness trials, and guiding the management of individual patients to prevent adverse outcomes in subsequent pregnancies. ■

ACKNOWLEDGMENTS

I thank Kurt Benirschke and Shirley Driscoll for encouraging a life-long interest in placental biology.

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