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# Placental pathology is necessary to understand common pregnancy complications and achieve an improved taxonomy of obstetric disease

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## Abstract

The importance of a fully functioning placenta for a good pregnancy outcome is unquestioned. Loss of function can lead to pregnancy complications and is often detected by a thorough placental pathologic examination. Placental pathology also has the potential to advance the science and practice of obstetrics and neonatal-perinatal medicine by classifying diseases according to underlying biology and specific patterns of injury. However, many obstacles have in the past limited the broad incorporation of placental findings into both clinical studies and day-to-day practice. Amongst the most serious limitations have been variability in the nomenclature used to describe placental lesions, a shortage of perinatal pathologists fully competent to analyze placental specimens, and a troubling lack of understanding of placental diagnoses by clinicians. This has led to a general lack of rigor in demanding best practices regarding placental submission, timely reporting of accurate pathology, and the incorporation of placental diagnoses into the management of both mother and infant. Yet the potential utility of placental pathology for phenotypic classification, improved understanding of the biology of adverse pregnancy outcomes, development of treatment and prevention, and patient counseling has never been greater. This review, written partly in response to a recent critique published in a major obstetric journal, is an attempt to reexamine the role of placental pathology by reviewing current concepts of biology, explaining the most recent terminology, responding to questions regarding utility, previewing upcoming changes in recommendations for placental submission, and suggesting a path forward. This path should include considerations of overall health care costs and cost effectiveness, the clinical value-added of placental assessment, improving placental pathology education and practice, and leveraging placental pathology to identify new biomarkers of disease and evaluate novel therapies tailored to specific clinicopathologic phenotypes of both women and infants.

### Keywords

acute chorioamnionitis; biomarker; diagnosis; funisitis; chronic chorioamnionitis; villitis of unknown etiology; chronic histiocytic intervillositis; cost effectiveness; economic analysis; massive perivillous fibrin; maternal vascular malperfusion; fetal death; fetal growth restriction; fetal vascular malperfusion; immunohistochemistry; infection; inflammation; placental abruption; preeclampsia; preterm birth; recurrent pregnancy loss; small for gestational age; stillbirth; thrombosis

## Introduction

Several recent developments make it timely to review why we do placental pathology and how we can improve and extend its value. First, the Amsterdam Placental Workshop Group consensus statement regarding diagnostic criteria and nomenclature for placental pathologic diagnoses, published in 2016, has become a benchmark, required for all placental pathology studies, and has led to significant advances in our understanding of adverse pregnancy outcomes (Box).[1] Second, a recent critique by Polnaszek et al[2] has expressed significant skepticism regarding the usefulness of placental pathology. These authors have

raised several important issues, and this review is, in part, a specific reply to each of the challenges they raise. Third, the perinatal and practice committees of the Society for Pediatric Pathology (SPP) following the input from several clinical societies (see the section on Revised indications for placental examination) recently solicited a draft proposal for a new and revised set of triage indications for placental examination that update and refine previous less specific guidelines published in 1997.[3] These recommendations, currently completing final committee review, will refine and clarify previous recommendations and prompt further inquiry into the diagnostic yield of each indication.

Two extreme views have constrained the use of placental pathology. One nihilistic perspective holds that placental pathology is of little or no value, while the other expresses blind faith that the answer to every outcome lies in the placenta, if only we understood it better. The truth is that, as with all other organ systems, specific underlying biologic processes lead to histopathologic patterns of injury that contribute to adverse outcomes. Not every adverse pregnancy outcome is explained by placental pathology, and not every placental lesion will lead to clinical consequences. However, some placental lesions provide immediate specifically actionable information, others predict possible recurrence in subsequent pregnancies, and many explain antenatal findings or postnatal adverse outcomes. Although placental pathology can help direct counseling and certain interventions in future pregnancies to improve outcomes, specific interventions are still limited. Future advances depend on identifying clinicopathologic phenotypes more reflective of the underlying biology. Defining the pathologic component of these phenotypes requires standardized submission of placentas for histopathologic examination.

This review addresses 6 specific topics. First, we provide a brief overview of the four major patterns, defined in the Amsterdam consensus, as a basis for understanding the modern clinicopathologic synthesis of the underlying biology causing placental injury. Second, we address why we examine placentas, earnestly reviewing the potential benefits and clinical utility. Third, we reiterate the importance of placental pathology for patient-centered care in obstetrics and neonatology. Fourth, in the context of the preceding discussion, we address the major concerns raised by the recent critique of Polnaszek et al.[2] Fifth, we preview newly proposed criteria for placental submission and discuss how they should evolve going forward. Finally, we outline our vision for the future of placental pathology, one centered around improving diagnostic reliability, more effective communication of patient results to treating physicians, better understanding of the clinical implications of placental diagnoses, more engagement with patients, and the expanded use of pathology for defining new clinicopathologic phenotypes through continuing basic and translational research using patient material and data.

## The Amsterdam consensus and the modern synthesis of placental pathology

The recently issued Amsterdam consensus statement provides uniform diagnostic criteria for the specific findings of clinical value that justify formal placental evaluation.[1] Although it is not possible to review all of placental pathology, we began this review with a brief overview

of the four most important patterns of placental injury as defined by the Amsterdam workshop group followed by a summary of the areas where improvement is necessary. Definitions for additional lesions referred to in the text and tables are provided in the Glossary.

Placental pathology, to a first approximation, can be separated into vascular and inflammatory categories (Table 1).[4] Vascular pathology encompasses distinct maternal and fetal subgroups, each of which includes early developmental abnormalities, later malperfusion-related lesions, and more acute losses of vascular integrity. Furthermore, acute and chronic Inflammatory lesions are separated into two subgroups, infectious and idiopathic.

Maternal vascular malperfusion (MVM) (previously termed uteroplacental insufficiency) is the histopathologic consequence of the failure of the extravillous trophoblast to implant deeply in the uterus and remodel the spiral arteries in early pregnancy. It is closely linked to the so-called “great obstetric syndromes” including preeclampsia, fetal growth restriction (FGR), and indicated preterm birth.[5,6] The pathophysiology is not completely understood and likely involves both genetic and environmental components. Most investigators in the field agree that insufficient uterine vascular remodeling leads to abnormal placental perfusion, reducing placental growth, contributing to oxidative stress, and increasing the risk of premature uteroplacental separation.[7–9] The Amsterdam consensus highlights key features of MVM including decidual arteriopathy, accelerated villous maturation, villous infarction, and abruptio placenta. Some pathologists include massive perivillous fibrin deposition (maternal floor infarction) in this category. However, this poorly understood lesion can also accompany inflammatory processes, both infectious and idiopathic.[10] Adverse outcomes associated with MVM include stillbirth and fetal death, FGR, and preterm delivery, both indicated and spontaneous.[11–15] As FGR is inconsistently defined by varying thresholds of infant birthweight for gestational age, the presence of placental MVM with or without clinically defined FGR may serve as a better marker of chronic fetal hypoxia, which can affect multiple developing organ systems including the fetal lungs, kidneys, brain and cardiovascular systems.[16] For example, placental MVM has been reported as a predictive marker of neonatal complications such as chronic lung disease and pulmonary hypertension.[17] Overall recurrence risk for MVM was relatively modest (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.3–1.9) in one recent study.[18]

Fetal vascular malperfusion (FVM) is most commonly caused by obstructed umbilical blood flow (the so-called “umbilical cord accidents”).[19,20] Obstruction can lead to vascular stasis, which promotes fetal vascular thrombosis.[21] Less commonly, fetal thrombi develop because of a prothrombotic state or damage to the endothelium or vessel wall, but even in these circumstances, stasis may be a contributing factor. Potentially obstructive umbilical cord abnormalities that become critically limiting in some pregnancies include excessive length, hypercoiling, fetal entanglements, peripheral insertion, and tethering by restrictive folds of amnion. Histopathologic findings in FVM include luminal thrombi, alterations to the wall of large fetal vessels, and a significant number of downstream avascular villi. Fetal vascular malperfusion is a recognized cause of stillbirth and fetal death and central nervous system (CNS) injury but is generally a sporadic lesion without significant recurrence risk.[22–25]

Acute chorioamnionitis is the histopathologic signature of placental bacterial or fungal infections, usually caused by organisms ascending from the cervicovaginal tract. It is defined by a neutrophilic infiltrate within placental tissues, most commonly elicited by so-called pathogen-associated molecular patterns.[26–33] This response has two components, maternal cellular inflammation in the placental membranes and chorionic plate and, less consistently, fetal cellular inflammation in the large fetal vessels and surrounding tissues of the umbilical cord ("funisitis") and chorionic plate. Some authors also recognize a category of "sterile" histologic chorioamnionitis defined by the inability to detect bacterial ribosomal RNA by polymerase chain reaction (PCR) and perhaps caused by non-pathogen-related "damage associated molecular patterns."[34–36] The criteria for assessing the duration and severity of inflammation are important but beyond the scope of this review.[37] Involvement of umbilical arteries and confluent (high-grade) inflammation of the chorionic vessels are known risk factors for fetal injury and neonatal complications.[25,38–40] Adverse outcomes include spontaneous preterm delivery and a ten-fold increase in the risk for neonatal sepsis.[15,41] Recurrence risk, after premature delivery, is relatively common (OR, 2.4; 95% CI, 1.2–4.7) and often related to maternal factors such as cervical insufficiency.[42] Hematogenous infections are rare but important causes of stillbirth and fetal death, FGR, and CNS injury and result in a different type of placental pathology, typically a villitis. Examples of hematogenous placental infections, often clinically unsuspected, that can be identified by histopathology include cytomegalovirus (CMV), syphilis, *Listeria monocytogenes*, and the recently described SARS-CoV-2 placentitis.[43–46]

Villitis of unknown etiology (VUE) is widely believed to represent a "host versus graft" (maternal antifetal) response caused by maternal T lymphocytes entering the fetal villous stroma where they become activated by fetal alloantigens leading to significant chronic inflammatory tissue damage.[47–49] Low-grade VUE is frequent and has limited clinical significance, but more extensive, high-grade disease is often associated with FGR and less commonly with stillbirth and fetal death and CNS injury.[50–52] Recurrence risk in subsequent pregnancies is high, 25% to 50%.[53,54] Idiopathic chronic inflammatory lesions in other regions of the placenta, including chronic chorioamnionitis, lymphoplasmacytic deciduitis, chorionic histiocytic hyperplasia, and eosinophilic and T-cell fetal vasculitis, are all loosely associated with VUE but can also occur independently.[55–59] Chronic chorioamnionitis and multifocal idiopathic chronic inflammation are recognized causes of late spontaneous preterm delivery.[60,61] Chronic histiocytic intervillositis is distinct from the other idiopathic chronic inflammation. This uncommon lesion, sometimes overlapping with massive perivillous fibrin deposition (maternal floor infarction), is strongly associated with miscarriage, stillbirth and fetal death, FGR, and both spontaneous and indicated preterm delivery.[62,63] The recurrence risk of chronic histiocytic intervillositis exceeds 50% in some studies.[64]

Although the field has grown over the last few decades and many new placental lesions have been defined, insufficient attention has been paid to separating the most important lesions from others of more limited significance and to communicating these distinctions clearly and succinctly in the pathology report. Even among the more important lesions, it is often unclear just how severe they are (i.e. high grade versus low grade, where high grade signifies a lesion or set of lesions sufficient by itself to cause a significant adverse

outcome). Researchers are actively pursuing these issues, and continuing work to refine placental classification to better predict clinical outcome is crucial for progress in the field. Of note, two approaches have recently been proposed. The first defines high-grade categories based on the extent and severity of individual lesions.[50] The second builds on the frequent observation that the finding of multiple placental lesions is a strong risk factor for adverse outcomes and constructs phenotypes based the number of individual lesions observed in several different pathophysiologic categories.[61] Going forward, both approaches need to be incorporated with other variables such as chronicity, activity, and the results of ancillary techniques to further subcategorize more general patterns of injury.

## Clinical utility: why do we examine placentas?

Having reviewed the underlying biology, the next important question is how can placental pathology improve patient care? In brief, placental pathology provides information useful for interpreting clinical signs and symptoms in the mother and infant, explaining abnormal antenatal testing, identifying treatable conditions, understanding adverse outcomes, predicting future complications, and guiding subsequent clinical care (summarized in Table 2). This information serves not only the obstetrician-gynecologist but also the interests of patients and other relevant specialties, such as neonatology, child neurology, and clinical genetics, who value the data provided in placental pathology reports.

## Obstetrical implications

The most familiar role of placental pathology is to help explain clinical findings and adverse outcomes in the index pregnancy and to guide the subsequent diagnostic work-up. Placental pathology currently serves the same role that the autopsy did in the era before sophisticated imaging and other diagnostic modalities. There is currently no effective technology capable of identifying important histopathologic processes in the placenta, so we rely on pathologic evaluation to identify these lesions. Placental pathology is most like to provide explanatory data in two situations: acute and unexpected adverse outcomes (birth asphyxia, depressed five-minute Apgar score, neonatal encephalopathy, sick neonate in the neonatal intensive care unit (NICU), and critically ill mother) and chronic and unexplained adverse outcomes (FGR, discordant twin growth, stillbirth and fetal death, neonatal or maternal death, recurrent fetal loss, and spontaneous preterm delivery). Table 3 provides lists of differential diagnoses pertinent to some of these outcomes. Other placental findings, such as placental malignancy (intraplacental choriocarcinoma or metastases) or a fragmented, possibly incomplete, placenta, or findings consistent with placenta accreta spectrum may lead to changes in the immediate management of the mother.

Some placental diagnoses identify maternal disease processes that may recur in subsequent pregnancies. Placental diagnoses with a substantial recurrence risk are listed in Table 2. Although specific interventions to prevent recurrent are currently limited,[65,66] it is important that parents be fully informed of their recurrence risk, that subsequent pregnancies be closely monitored, and that cases be documented for future studies to develop better diagnostics and more effective treatments. Several novel treatments applicable to MVM have been proposed.[67–69] Other potential therapeutic approaches targeting the underlying pathogenesis of FGR, an often-recurrent adverse outcome, have recently been reviewed.[70]

## Neonatal implications

Providers of obstetrical care concerned with the relevance of placental pathology to the mother sometimes forget the importance of placental findings for the management of the newborn. It is not uncommon to identify immediately treatable conditions ("critical values") that, when communicated expeditiously, may lead to potentially lifesaving interventions. The importance of such findings is the impetus for shortening the turnaround time for placental pathology. Examples include hematogenous infections, such as CMV, listeriosis, or SARS-CoV-2 placentitis; placental thrombi that may indicate a coagulopathy in the newborn; histologic chorioamnionitis, which increases the risk of neonatal sepsis; candida funisitis in an infant not currently on antifungal therapy; and fetal genetic conditions, such as lysosomal storage diseases or Bartter syndrome. Moreover, there is considerable use in the finding of a "normal placenta" in ruling out several newborn complications, such as bacterial sepsis and seizures presenting with soft signs, such as neonatal apnea and bradycardia. Reassurance of a normal placenta, if interpreted correctly and in the context of the clinical presentation, can also potentially shorten NICU length of stay.[41] An important priority is to ensure that all providers of neonatal care fully understand the potential use of placental pathology.

## Long-term implications

Placental findings also have implications for the long-term health of both mother and child. Several placental lesions are risk factors for later non-pregnancy-related diseases and can identify patients who could benefit from increased surveillance and therapeutic interventions. High-grade placental MVM may be a predictor of high-risk early maternal cardiovascular disease and developmental programming of adult-onset diseases of the newborn.[71–73] Other placental lesions such as chronic histiocytic intervillositis, massive perivillous fibrin, and decidual vascular thrombi, can be the first indicators of maternal autoimmune diseases, including the antiphospholipid antibody syndrome.[74,75] Preterm infants whose placentas have amnion nodosum, subacute chorioamnionitis, MVM, abnormal placental vascularization, and diffuse chorioamnionic hemosiderosis, are at increased risk for chronic lung diseases.[17,76–79] Finally, as discussed above, term infants with high-grade fetal vascular pathology are at increased risk for the later development of seizure disorders, developmental disability, and static neuromuscular conditions such as cerebral palsy.[51]

## Quality assurance

Clinical diagnoses, such as abruption or intra-amnionic inflammation, can be confirmed, excluded, or clarified by placental examination. New diagnoses and pathologic conditions may emerge. The timing of various events can be estimated. Other clinical conditions, such as severe preeclampsia, poorly controlled maternal diabetes mellitus, polyhydramnios, recurrent periviable preterm delivery, other infections, and hydrops fetalis may be better explained. All of these placental findings provide useful feedback to the individual practitioner, inform the discussion at clinical morbidity and mortality conferences, and document important pathophysiological processes in the electronic medical record that may assist in risk management or affect future pregnancies.

## Placental pathology in low-risk pregnancies

In a world with unlimited resources, we might send all placentas to pathology.[80] However, in the United States today, it is important for clinical care providers to be familiar with situations where routine placental examination, in the absence of other indications and outside of a research setting, is less likely to provide crucial additional information. These include, in our experience, common genetic, chromosomal, and malformation syndromes already well classified by antenatal testing, patients with previous adverse outcomes but no abnormalities in the present pregnancy, insufficient or absent prenatal care with a well newborn, and underlying medical disorders without acute exacerbations during pregnancy. A recent study added well-controlled gestational diabetes mellitus or chronic hypertension, maternal obesity, and recent meconium release to this list.[50] In general, there are few instances where a non-acutely ill mother, without previous placental pathologies, delivering a singleton term or near-term birth with normal birthweight, a 5-minute Apgar score of $\geq 7$, and a normal-appearing placenta will benefit from a comprehensive histopathologic placental examination. We believe that if placentas in these situations were no longer sent to pathology, the overall rate of submission might be substantially reduced.

## Importance of placental pathology for patients and patient-centered care

No discussion of the benefits of placental pathology would be complete without considering the value of placental pathology for the patient. Mothers and families naturally want to know why they have suffered an adverse pregnancy outcome. In the absence of a pathologic examination, the most honest answer by the obstetrician would have to be “I am not completely sure,” which is deeply unsatisfying for everyone involved. It would be a mistake to think that patients are unaware of placental pathology. Pathologists frequently receive questions from patients with a quite sophisticated knowledge of their placental pathology. Furthermore, patient advocacy groups are very aware that many obstetricians do not fully understand or value placenta pathology, and they have asked legitimate questions as to why these findings are not incorporated into clinical care (personal communication, Fernanda Sheridan, PUSH for Empowered Pregnancy).

However, there are so many potential benefits to be gained by engaging patients with placental pathology. Patients feel empowered when they know more about their pregnancies, past and present. Their general health literacy and specific knowledge of their bodies is enhanced. They realize that others share the same problems. They feel that they can be fully informed participants in future care decisions. Discussion of the placental pathology report can enhance respect for the obstetrician and the field as a whole. There is no feeling that information is being withheld or that there might be discord between specialties. To be sure, there are obstacles as well, and recent studies have addressed the importance of better placental pathology reports with patient-centered comments using lay language.[61]

Awareness of placental pathology by patients has less direct benefits as well. A personal diary of past pathology regarding miscarriages and adverse outcomes across reproductive life can overcome the obstacles of fragmented care by multiple medical care providers. Patients sharing recurrent adverse outcomes associated with specific placental lesions can be powerful advocates for increased funding for research in the field and may participate

in national or international patient registries. These registries can be leveraged to provide the two main requirements for contemporary multi-omics research studies: well-defined phenotypes and large numbers. Such patient-centered research has led to major advances in other fields and can serve as an essential step toward the holy grail of 21st-century practice, truly personalized medicine.

## Recent critique questioning clinical practice regarding placental examination

Not everyone agrees that there is value in submitting placentas for pathologic examination. A wide-ranging critique recommending a drastic reduction in the number of placentas submitted for pathologic assessment was published by three prominent obstetrician-gynecologists in the March 2022 issue of *Obstetrics & Gynecology*.[2] The authors began with a clinical vignette: a patient with gestational diabetes mellitus requiring insulin therapy who delivers an enlarged placenta with the unexpected finding of a “velamentous” (membranous) umbilical cord insertion. This placenta is sent to pathology according to “tradition” without any clear understanding of what might be learned. Of note, two relevant questions are raised in this case. First, does every placenta from a mother with diabetes mellitus need to be sent to pathology? The answer according to recent studies is maybe not; only those from poorly controlled (clinically or by large for gestational age or heavy placenta >90th percentile) or pregestational diabetes mellitus are likely to show clinically relevant abnormalities.[50,81] Second, could the obstetrical team just document the membranous or velamentous insertion of the umbilical cord in this normal infant without incurring pathology charges? The answer is “yes,” as explained above, but membranous or velamentous umbilical cord insertion is a known risk factor for placental FVM, which can lead to abnormalities, such as neonatal stroke that may present in the days and weeks after birth.[82] The point is that, even in this purportedly straightforward example, the decision of whether to submit the placenta is not simple, and the cost-benefit of formal placental evaluation in each such circumstance needs to be thoughtfully considered.

The authors estimated that approximately three-quarters of a million placentas undergo complete pathologic evaluation in the United States every year. The submission rates have gradually increased from approximately 10% to 15% in the early 1990s to 20% to 25% to date.[83] This increase has been coincident with major advances in diagnostic placental pathology and is the greatest in centers specializing in high-risk pregnancies. Community hospitals without experienced perinatal pathologists often have lower submission rates, and this together with inadequate placental pathology reports has been cited as a significant impediment to clinical care for cases referred from such hospitals for tertiary care.[84] Although opinions vary, it is possible that the number of placentas currently examined could be reduced without clinical consequences. However, as with other obstetrical testing, submission rates should be driven by updated, evidence-based recommendations rather than a subjective impression that too many placentas are being examined.

Regarding the reasons for increased submission, the authors suggested that it is largely pathology driven—beginning with the 1997 College of American Pathologists (CAP) guidelines for placental pathology practice. However, these guidelines were drafted by a multidisciplinary task force that included three pathologists, two maternal-fetal medicine

(MFM) specialists, one neonatologist, and two obstetrics-gynecology physician assistants.[3] Furthermore, this report merely formalized suggestions published in textbooks and review articles beginning in the late 1980s. The authors made several additional observations. First, the absence of a formal American College of Obstetricians and Gynecologists (ACOG) endorsement of the recommendations indicates that placental pathology is not worthwhile. Second, the failure of the rates of prematurity, cerebral palsy, perinatal mortality, and malpractice costs to decrease since the 1997 CAP recommendations is evidence that placental pathology is not useful. Third, confusion and lack of knowledge regarding the CAP guidelines suggest that placental pathology provides little value. We find these arguments less than compelling. However, the authors asked four additional questions that deserve further discussion.

**a.** *"How predictive are placental abnormalities of long-term adverse neurologic outcomes"?* The authors essentially set up a "straw-man" by stipulating that (1) only large population-based studies are acceptable, (2) confounders must be fully accounted for in the study design, (3) associations are not sufficient, causality must be proven, and (4) even if causality is proven, this information must lead to improvements in clinical care. Very few clinical laboratory tests could fulfill this daunting list of requirements. However, if we examine the question more closely, the answer is straightforward. There is no credible claim that placental abnormalities, in and of themselves, are *predictive* of long-term adverse neurologic outcomes. Relatively, the argument is the converse. First, in multiple appropriately controlled cohort studies, certain specific placental abnormalities are strongly associated with CNS injury (i.e. common in cases and rare in controls). Second, in the absence of other identifiable causes, these abnormalities are both necessary and sufficient to explain the observed outcomes. To use a more familiar example, most individuals suffering a myocardial infarction do not die, but when an elderly person is found dead at home, the post-mortem pathological finding of a myocardial infarction is reasonably considered to be the cause of death. Although we have acknowledged the methodologic arguments that some epidemiologists have raised against non-population-based studies, we would argue that the perfect should not be the enemy of the good. There are several high-quality, recent cohort studies that show strong associations between placental pathology and CNS injury. To briefly summarize this literature, in term infants, high-grade lesions, including FVM, VUE, acute chorioamnionitis with severe fetal inflammatory response, and meconium-induced myonecrosis, have shown strong associations with cerebral palsy, neonatal encephalopathy, and CNS abnormalities as detected by early MRI.[24,85] In preterm infants, acute chorioamnionitis with high-grade fetal inflammatory response, diffuse placental edema, severe MVM, and having more than one placental lesion have shown strong associations with cerebral palsy, epilepsy, autism spectrum disorders, and cognitive impairment.[38,86–88]

**b.** *"In what situations or conditions are placental abnormalities useful for subsequent pregnancy management after an adverse obstetrical outcome"?* The authors argue that despite the ability of placental pathology to identify placental

lesions causing adverse pregnancy outcomes with substantial recurrence risks and to determine the etiology of stillbirth and fetal death, it is essentially pointless since there are few currently effective preventative therapies. A similar line of reasoning would suggest that performing routine diagnostic biopsies of malignancies 50 years ago was inappropriate because there were few effective cancer treatments. It is difficult to envision how the field moves forward with such a nihilistic perspective. We would argue that there are some currently useful interventions (see the section on Clinical utility: why do we examine placentas?) but acknowledge that fully effective personalized medicine for specific obstetrical disorders is not yet available and is an urgent priority. As discussed in the final section, placental pathology is an essential tool for realizing this goal.

**c.** *"Do placental findings provide useful information in medicolegal-litigation"?* After a PubMed search of the medical literature, the authors conclude "that the supposition that placental pathology, at least in and of itself, can help with few claims of medical negligence related to adverse childhood neurologic[al] status is based on either anecdotal evidence or evidence that has not found its way into the medical literature." However, such studies do exist in the medical literature, and a search of the legal literature using tools like LexisNexis would likely yield additional support.[89] The authors continued to express the opinion that "placental pathology findings are very rarely influential," because "for every pathologist making [one] claim, another will generally refute it." The latter statement, of course, applies equally to expert witnesses in obstetrics, child neurology, neuroradiology, and neonatology. On the contrary, the pathologist authors of this review, having reviewed hundreds of medicolegal cases, and the attorneys we have worked with felt strongly that placental pathology has played a determinative role in many cases. Other perinatal pathologists have published similar opinions in the peer-reviewed literature.[90,91]

**d.** *"What are the monetary costs of formal placental evaluation?"* The authors opine that the costs of placental pathology, up to 209 million dollars per year, are excessive. Subjective claims regarding excessive health care costs are, of course, arbitrary and need to be justified by quantitative data. Compared with other diagnostic tests and procedures routinely obtained on obstetrics patients, the price of a placental evaluation is relatively modest. The most recent charge reported by the authors ($290 per placenta) is standard for all large non-neoplastic pathology specimens and reflects technical and professional labor, reagent costs, and the overhead required for processing and diagnosis. It is the same as would be charged for a benign hysterectomy for dysmenorrhea. Although controlling health care costs is an urgent priority, the more relevant questions are the cost-benefit and value added of a comprehensive placental examination for mothers in specific clinical situations.

As stated above, the authors of this critique recommend a drastic reduction in the number of placentas submitted for pathologic examination. However, before tossing placental pathology aside, we should at least understand what we would be losing. The authors

cited a recent survey reporting that only 21% of obstetrician-gynecologists understand their placental pathology reports[92]; the percentage among similarly informed pediatricians caring for high-risk newborns remains unreported. There is perhaps no other field of medicine where such a failure to communicate is accepted. We believe that the underlying problem is an unfortunate lack of full engagement with placental pathology by many pathologists, obstetricians, and neonatologists, in part, because of an incomplete knowledge of each other's specialties. As described by the authors, the decision by the obstetrical care provider to send the placenta to pathology is made quickly after delivery, roughly guided by previous experience, how complicated the pregnancy was, the perceived risk of litigation, and incomplete knowledge of published practice guidelines and their institutional policies. Very little thought goes into what information might be gleaned, what specific pathologic diagnoses mean, or how to integrate this information with other data to guide subsequent care. A similar lack of critical thinking on the part of neonatal care providers regarding how to use data from this vital organ of pregnancy may also hamper the care of the infant. Finally, pathologists have constructed elaborate classification systems and conducted studies with limited clinical input, published in journals not widely read by most obstetrician-gynecologists and neonatologists. Moreover, the quality of placental pathology reports across the United States is uneven. General pathologists often lack specific training in perinatal pathology and may be unaware of the most recent guidelines. There seems to be ample room for improvement on all sides.

## Revised indications for placental examination

The preceding discussion naturally points to the need for improved and clearer guidelines to help physicians and midwives decide which placentas to submit to pathology. This decision should consider several factors, including the cost to the patient, the potential information to be gained, and how this information might be used. Although histopathology offers great potential for advancing the science of obstetrics, placental pathology is performed as a laboratory test and not a research tool. Prospective, population-based, and fully controlled studies require other sources of funding. As discussed above, the current guidelines for placental submission were published in 1997. Several significant international collaborative groups, including the SPP Nosology project, the Amsterdam International Consensus group, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Stillbirth Collaborative study investigators, have refined and advanced placental diagnostic pathology since that time.[1,93–96] A recent study examined the yield of high-grade placental pathology in term infants for each of the CAP indications and identified several common CAP indications that are not strongly associated with significant placental findings.[50] Based on new evidence and changes in clinical practice, a revised and more stringent set of indications for placental submission was identified as a priority by the Perinatal and Practice Committees of the SPP. A panel of 16 perinatal pathologists and allied professionals, using a modified Delphi procedure, has proposed updated recommendations that have been endorsed by the SPP, the ACOG, and the Society for Maternal-Fetal Medicine. The new recommendations fall into six categories: placental gross findings, antepartum maternal complications, antepartum obstetrical indications, antepartum fetal indications, intrapartum complications, and neonatal indications. Complete presentation of

these new guidelines awaits final committee approval by the Neonatal-Perinatal Section of the American Academy of Pediatrics (manuscript in preparation).

## Future perspectives: the way forward

An important component of reinvigorating placental pathology is to improve day-to-day clinical practice. Establishing simple, realistic, mutually agreed upon recommendations for submission that are continually reevaluated is the starting point. As not all specimens can be submitted or representative tissues banked, there should be a system for holding placentas in the refrigerator for several days after delivery in case the condition of the mother or baby deteriorates after delivery. As it is not feasible for the pathologist to review the electronic medical record for every specimen, a summary of the clinical scenario is necessary. This should be provided by the obstetrician or midwife, not ancillary staff, and should include specific questions. Ideally, every placenta would have the relevant indication(s) for a submission selected from a prepopulated checklist based on the most current recommendations. The format of pathology reports should be improved and standardized with the most important patterns highlighted and graded and less important findings clearly demarcated. A synoptic format with mandated checklists may be necessary. The judicious use of notes and comments to explain the significance of findings to the clinician and the parents is also to be encouraged. Timeliness of reporting is crucial. Placental diagnoses should ideally be in the electronic medical record within 48 to 72 hours of receipt. Placentas from infants in distress or admitted to the NICU should be prioritized, and a pathway for communicating “critical values” (see the section on Clinical utility: why do we examine placentas?) needs to be established. Appropriate and uniform clinical follow-up for important placental diagnoses should be tracked, documented, and discussed at regularly scheduled interdepartmental conferences.

Of note, two more general goals are to improve the overall quality of perinatal pathology practice across the United States and to increase the understanding of placental diagnoses by clinical providers. Concerning the former, consideration of perinatal certification as part of pathology fellowships training should be encouraged, and rotations for senior pathology residents planning to assume responsibility for perinatal pathology in their subsequent positions should be established and standardized. Concerning the latter, better review articles, textbooks, and web-based applications oriented to clinicians are needed. Placental pathology education should be incorporated into the national meetings of obstetrician-gynecologists and neonatologists, the local didactic and case-oriented clinical conferences, and the rotations of obstetrics-gynecology residents and MFM and neonatology fellows. Placental pathology questions should also be a part of resident in-service examinations and specialty board examinations for pathologists, obstetrician-gynecologists, and neonatologists.

Most obstetrical syndromes are defined by clinical presentation alone. However, there are many other potentially useful sources of data, including improved imaging, biochemical testing, analysis of gross placental measurements, and placental histopathology with standardized grading, scaling, and focused subsequent ancillary testing. All can contribute to creating more robust clinicopathologic phenotypes and building a new “taxonomy

of obstetrics." Focusing on MVM as an example, an important consequence of this pattern is oxidative stress leading to syncytiotrophoblast damage and the release of plasma membrane fragments, extracellular vesicles known as exosomes, into the maternal circulation. These exosomes contain cellular RNA and are detectable as early as the first trimester of pregnancy. The analysis of their concentration and composition in maternal blood may predict MVM, months before delivery.[97–101] A recent study combining abnormal histopathology (MVM) and abnormal maternal serum soluble fms-like tyrosine kinase-1 (sflt-1) and placental growth factor (PlGF) revealed previously unappreciated subsets of patients with PPROM and preterm labor and allowed FGR and preeclampsia to be predicted several weeks earlier than angiogenic markers alone.[102] Using exosomes together with serum sflt-1 and PlGF to predict MVM might improve risk assessment. However, not all cases of preeclampsia are associated with histopathologic changes of MVM. Bainbridge and Cox, using a combination of placental histopathology and transcriptome analysis, identified three distinct subgroups of preeclampsia and small-for-gestational-age (SGA) infants, one with MVM, an inflammatory subgroup with features of VUE and increased perivillous fibrin, and another with no histopathologic abnormalities.[103,104] Such studies have only begun to unravel the heterogeneity of these obstetrical syndromes. To achieve the new taxonomy we seek, placental pathology must be integrated, along with novel imaging and molecular techniques, into future National Institutes of Health-supported clinical trials.[105] A recent review highlighted the additional benefits that might have accrued if placental pathology had been incorporated into previous clinical trials.[106]

Future progress in placental pathology will likely require moving beyond routine histology. Several ancillary techniques not yet fully validated for clinical diagnosis can provide additional information. These include bacterial ribosomal 16S RNA qPCR for; chorioamnionitis, sflt-1, AP-2, and p63 immunohistochemistry (IHC) for MVM; CD34 IHC and iron stain for FVM; CD15 IHC for delayed villous maturation; caspase-3 IHC for meconium-induced myonecrosis; CD138 IHC for lymphoplasmacytic deciduitis; and C4d, CD3, and other T-cell markers by IHC for VUE.[27,107–117] However, we also need to incorporate state-of-the-art methods currently being applied elsewhere in pathology. These include both *in vivo* and *ex vivo* imaging, multiplex and multi-omics in situ hybridization and immunohistochemistry (using novel digital spatial profiling and mass cytometric methods), and single-cell profiling (for both transcriptome and chromatin landscape analysis).

A lack of appreciation of placental pathology goes hand-in-hand with a lack of understanding of the basic biology of this important organ. Nowhere else in the study of human disease is an organ so under-studied and poorly defined, both at the cellular and molecular levels, particularly given its critical role in the health of both women and children. Amongst the biologic questions potentially addressed by a better understanding of placental cellular composition and molecular activation state across gestation are regulation of villous maturation, capillary density, fetal vascular contractility, regenerative capacity, and trophoblast pathology. A recent study of first-trimester placentas using multiparameter flow cytometry with single-cell RNA sequencing data revealed a previously unrecognized placental leukocyte subset.[118] This population, termed the placenta-associated maternal macrophage (type 1a), is restricted to the intervillous space and is postulated to function

during villous repair. These cells might play an important role in poorly understood placental diseases, including VUE, chronic histiocytic intervillositis, placental infections such as falciparum malaria and SARS-CoV-2, and the “immunologic” molecular subgroup of preeclampsia.[64,103,104,119–121] Similar studies have revealed new subtypes of decidual immune cells[122], a unique lymphatic or endothelial cell type in fetal membranes that could explain local trafficking of maternal lymphocytes,[123] and key cell-to-cell networks involved in maternal-fetal communication.[124] Additional funded projects to create complete atlases of placental cell types by single-cell RNA sequencing and spatial transcriptomics are currently underway.

## Conclusions

Perhaps pathologists and clinicians can agree on several priorities: (1) Indications for placental submission need to be widely disseminated and clearly understood by everyone, (2) pathologists must apply consensus criteria and more effectively communicate the meaning of placental lesions, (3) clinicians should demand more uniformly acceptable placental reports across the United States, (4) clinicians must learn basic placental diagnostic terminology or contact the pathologist when terms are used that they do not understand, and (5) placental diagnoses need to be integrated with clinical data. Until these issues are addressed, the questions raised by Polnaszek et al[2] cannot be fully answered.

We think that the continuing evaluation of placental pathology is crucial not only for clinical practice but also for future progress in clinical, translational, and basic research in obstetrics and neonatology. We need a better understanding of placental development across gestation and of the underlying etiology of adverse pregnancy outcomes. The Human Placenta Project funded by the NICHD has prioritized the development of new biomarkers to identify placental diseases early in pregnancy and of therapeutics that permit targeted intervention to prevent serious complications, such as stillbirth/ and fetal death, FGR, and preterm labor.[125] The few examples described in this review are only the beginning. The placenta has many secrets yet to be revealed, and placental pathology is the venue to better understand these relationships between structure and function and pregnancy outcomes. All of these goals depend on a culture that believes in the use and relevance of appropriately submitting placentas for pathologic evaluation.

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## Glossary of Terms

**Abruptio placenta**

Large destructive retroplacental hemorrhage because of rupture of a major spiral artery, often secondary to decidual arteriopathy

**ACOG**

American College of Obstetricians and Gynecologists

**Acute chorioamnionitis**
Cellular inflammation most often seen in response to amniotic fluid infection; defined by neutrophils in the chorion and amnion of the fetal membranes

**CAP**
College of American Pathologists

**Chorionic histiocytic hyperplasia**
Band of activated macrophages within the chorionic plate; usually accompanying high-grade villitis of unknown etiology

**Chronic abruption or oligohydramnios sequence**
Repetitive small marginal retroplacental hemorrhages because of disruption of maternal veins, often due to insufficient tissue support; commonly associated with subchorionic hemorrhage and/or vaginal bleeding in early pregnancy; accompanied by oligohydramnios in severe cases

**Chronic (lymphocytic) chorioamnionitis**
Increased lymphocytes in the chorion and amnion of the fetal membranes, thought to represent a “host versus graft” response of the mother against fetal antigens

**Chronic histiocytic intervillositis**
Diffuse infiltration of the maternal intervillous space by activated maternal macrophages; thought to represent an innate immune response to abnormal trophoblast, often recurrent in subsequent pregnancies (must rule out infectious origins, e.g., SARS-CoV-2 placentitis)

**CI**
confidence interval

**CMV**
Cytomegalovirus

**CNS**
Central nervous system

**Congenital infection**
Maternal hematogenous infection of the placenta; separated into villitis, caused by TORCH-type pathogens (toxoplasmosis, rubella, CMV, herpes and other agents), such as CMV, and intervillositis, caused by other pathogens including malarial parasites, *Listeria monocytogenes*, and SARS-CoV2

**Decidual arteriopathy**
Abnormalities of maternal spiral arteries; often associated with maternal vascular malperfusion; includes acute atherosis (fibrinoid necrosis), mural hypertrophy, and chronic perivasculitis, primarily affecting membranous arterioles, and persistent muscularization of basal plate arteries

**Delayed villous maturation or placental maturation defect**
Retarded maturation of terminal villi defined by increased diameter, excessive villous stroma, thickened villous trophoblast, and a lack of capillaries near the syncytiotrophoblast; associated with decreased efficiency; most commonly seen with diabetes mellitus and obesity

**Diffuse villous edema**
Large accumulations of extracellular fluid within the immature intermediate villi of placentas from very-low-birthweight infants

**Dysmorphic villi suggestive of developmental abnormality**
Villous features resembling those associated with certain chromosomal abnormalities; includes abnormal villous branching, irregular villous contour, villous stromal trophoblast inclusions, and an abnormal capillary vascular pattern

**Eosinophilic T-cell fetal vasculitis**
Idiopathic fetal chronic inflammatory response composed of fetal eosinophils and T cells infiltrating stem villous and chorionic vessels; sometimes associated with villitis of unknown etiology and fetal vascular malperfusion

**Fetal inflammatory response**
Cellular inflammatory response to amniotic fluid infection defined by neutrophils within the walls of fetal blood vessels, either in the umbilical cord (“funisitis”) or in the chorionic plate

**Fetal vascular malperfusion**
Obstructed fetal blood flow due to thrombosis and/or prolonged umbilical cord compression leading to avascular villi

**Feto-maternal hemorrhage**
Rupture of terminal villi, often clinically silent, with loss of fetal blood into maternal circulation; sometimes associated with intervillous thrombi and/or hydrops fetalis

**FGR**
Fetal growth restriction

**FVM**
Fetal vascular malperfusion

**Hydrops fetalis**
Fetal congestive heart failure, usually due to obstructed blood flow, hepatic insufficiency, or chronic anemia, leading to diffuse and marked edema of placental terminal villi

**IHC**
Immunohistochemistry

**Lymphoplasmacytic deciduitis**
Numerous maternal plasma cells in the decidua basalis, often associated with villitis of unknown etiology, previous bacterial endometritis, and/or idiopathic preterm labor

**Marginal abruption**
Acute marginal retroplacental hemorrhage due to rupture of maternal veins, often due to insufficient tissue support or acute inflammation (chorioamnionitis)

**Massive perivillous fibrin deposition or maternal floor infarction**
Diffuse infiltration of the maternal intervillous space by fibrin-type and matrix-type fibrinoid; sometimes accompanied by activated macrophages and complement components; thought to represent a response to injured trophoblast, often recurrent in subsequent pregnancies

**Maternal vascular malperfusion**
Defined by accelerated villous maturation: alternating areas of villous paucity and crowding with increased syncytial knots and focal intervillous fibrin; often accompanied by infarcts and decreased placental weight

**Meconium-induced myonecrosis**
Patchy-diffuse apoptotic cell death of vascular smooth muscle cells due to the toxic effects of longstanding meconium exposure; located at the periphery of large fetal vessels in the umbilical cord or chorionic plate

**Multifocal (high-grade) idiopathic chronic inflammation**
Chronic inflammation involving more than one of the following placental compartments: chorionic plate or membranes, basal plate, villous stroma, and fetal vasculature

**MVM**
Maternal vascular malperfusion

**NICHD**
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development

**NICU**
Neonatal intensive care unit

**Placental findings consistent with sentinel event**
Gross or microscopic evidence of extensive retroplacental and/or intravillous hemorrhage (e.g. abruptio placenta), complete umbilical cord occlusion (cord torsion or hypercoiling), or massive fetal or fetomaternal hemorrhage

**OR**
Odds ratio

**PCR**
Polymerase chain reaction

**PlGF**
Placental growth factor

**Sflt-1**

Soluble fms-like tyrosine kinase-1

**SPP**
Society for Pediatric Pathology

**Superficial implantation site**
Basal plate with abundant decidualized endometrial stroma and numerous placental site giant cells in the absence of invasive mononuclear extravillous trophoblast, fibrinoid, and vascular remodeling

**Villitis of unknown etiology**
Infiltration of chorionic villous stroma by small lymphocytes and activated macrophages, often accompanied by avascular villi and perivillous fibrin; thought to represent a “host versus graft” response of mother against fetal antigens

**Villous capillary proliferative lesions**
Multiple foci of villi with an increased number of capillaries (more than 10 cross sections or villus); separate associations with prolonged maternal hypoxemia and diabetes mellitus

**Villous stromal hemorrhage**
Recent tissue hemorrhage in the villous stroma due to acute hypoxia-induced capillary rupture; most commonly seen with abruption in preterm placentas

**VUE**
Villitis of unknown etiology

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**Text Box:**

### 2014 Amsterdam Consensus Conference: background and follow up

"Practicing perinatal pathologists and placental pathologists were invited to participate in a one-day workshop to derive recommended standards for placental examination and sampling and consensus agreement for diagnostic criteria for placental lesions. Research-active placental pathologists and maternal-fetal medicine specialists with a strong placental research interest were identified by a search of authors through PubMed and by reputation, while an open invitation was also issued through a global Pediatric Pathology e-web to all practicing perinatal pathologists. The group comprised 52 who were contacted directly; 40 expressed an interest in attending of whom 27 (68%) actively participated before the meeting by prioritizing placental pathology lesions for discussion and potential areas of controversy or uncertainty and opinions, which were then circulated prior to the workshop. Twenty six pathologists were able to attend and participate in the workshop held in Amsterdam, The Netherlands, in September 2014..." abstracted from the study introduction of Khong etal.[1]

Following the discussion and review of the published literature, the expert panel developed recommendations to standardize the definitions of lesions for four processes that constitute most clinically important placental pathologies: maternal vascular malperfusion, acute chorioamnionitis, fetal vascular malperfusion, and villitis of unknown etiology. These standards were published in 2016 and have served as an agreed upon basis for most subsequent placental clinical and research endeavors.[1] A second two-day meeting of the same group was held in Dublin, Ireland, in February 2018, which resulted in the publication of a comprehensive multi-authored textbook describing in more detail the entire range of placental pathology.[130]

**Table 1:**

Vascular and inflammatory categories of placental pathology with specific lesions

| Vascular and inflammatory categories |
|---|
| Maternal vascular |
| Maldevelopment |
| *decidual arteriopathy* |
| *superficial implantation site* |
| Malperfusion |
| *partial: accelerated villous maturation or distal villous hypoplasia* |
| *complete: villous infarction* |
| Loss of Integrity |
| *abruptio placenta (arterial)* |
| *marginal abruption, acute or chronic (venous)* |
| Fetal vascular |
| Maldevelopment |
| *delayed villous maturation* |
| *villous capillary proliferative lesions* |
| Malperfusion |
| *Partial: umbilical cord obstruction or small foci avascular villi* |
| *Complete: fetal thrombosis or large foci avascular villi* |
| Loss of integrity |
| *villous stromal hemorrhage* |
| *villous edema or hydrops fetalis* |
| Inflammatory, infectious |
| Acute bacterial or fungal |
| *chorioamnionitis with or without fetal vascular involvement* |
| *villitis or intervillositis* |
| Chronic viral/ protozoal |
| *villitis* |
| *intervillositis* |
| Inflammatory, idiopathic |
| *villitis of unknown etiology* |
| *chronic (lymphocytic) chorioamnionitis* |
| *lymphoplasmacytic deciduitis* |
| *chorionic histiocytic hyperplasia* |
| *eosinophilic or T-cell fetal vasculitis* |
| *chronic histiocytic intervillositis* |
| *massive perivillous fibrin deposition (maternal floor infarction)* |

**Table 2:**

Specific situations where placental evaluation can provide additional useful information

| Variable |
|---|
| Determine potential underlying causes of adverse outcomes |
| • Spontaneous preterm delivery |
| • Fetal growth restriction |
| • Stillbirth and fetal death |
| • Neonatal encephalopathy or suspected central nervous system injury |
| Identify immediately treatable processes (requires timely reporting of critical values) |
| • Mother: specific infections, retained placenta, malignancy: metastases, choriocarcinoma |
| • Infant: elevated risk of neonatal sepsis (histologic chorioamnionitis with fetal inflammatory response), specific infections (cytomegalovirus, Candida, syphilis, Listeria), fetal genetic diseases with placental phenotype (e.g. inborn errors of metabolism), fetal malignancy |
| Estimate recurrence risk (RR) in subsequent pregnancies |
| Common lesions: |
| • Villitis of unknown etiology (RR: 25% to 50%)53,54 |
| • Placenta accreta (RR: 10% to 25%)126 |
| • Maternal vascular malperfusion (RR: 10% to 25%)18 |
| • Preterm acute chorioamnionitis (RR: 10% to 25%)42 |
| • Placental abruption (RR: 4% to 5 %)127 |
| Uncommon lesions |
| • Chronic histiocytic intervillositis (RR: 75% to 90%)64 |
| • Massive perivillous fibrin/ maternal floor infarction (RR: 30% to 60%)128 |
| • Multiple chorangioma syndrome (RR: 35-40%)129 |
| Guide future care paths |
| • Genetic counselling |
| • Early high-risk referral |
| • Antenatal maternal blood screening |
| • Targeted placental ultrasound and Doppler studies |
| • Personalized therapy (ASA, progesterone, novel therapeutics) |
| Quality assurance and risk management |
| • Gold standard in specific clinical situations (e.g., chorioamnionitis and abruption) |
| • Uncovering subacute and chronic disorders predisposing to birth asphyxia, neonatal encephalopathy, seizures, stroke, or cerebral palsy |

**Table 3:**

Placental findings associated with specific adverse outcomes by gestational age in descending estimated order of frequency

| Findings |
|---|
| Spontaneous preterm birth |
| Early preterm (<34 weeks) |
| Acute chorioamnionitis |
| Marginal abruption |
| Lymphoplasmacytic deciduitis |
| Maternal vascular malperfusion |
| Late preterm (34–37 weeks) |
| Maternal vascular malperfusion |
| Acute chorioamnionitis |
| Chronic (lymphocytic) chorioamnionitis |
| Multifocal idiopathic chronic inflammation |
| Fetal growth restriction |
| Early preterm (<34 weeks) |
| Maternal vascular malperfusion |
| Chronic abruption or oligohydramnios sequence |
| Massive perivillous fibrin deposition |
| Dysmorphic villi suggestive of developmental abnormality |
| Term and late preterm (34–42 weeks) |
| Maternal vascular malperfusion |
| Villitis of unknown etiology |
| Fetal vascular malperfusion |
| Central nervous system injury |
| Early preterm (<34 weeks) |
| Acute chorioamnionitis with high grade FIR or chorionic vessel thrombi |
| Diffuse villous edema |
| Term and late preterm (34–42 weeks) |
| Fetal vascular malperfusion |
| Villitis of unknown etiology with obliterative fetal vascular changes |
| Acute chorioamnionitis with severe fetal inflammatory response |
| Meconium-induced myonecrosis |
| Placental findings consistent with sentinel event |
| Stillbirth and fetal death |
| Early preterm (<34 weeks) |
| Maternal vascular malperfusion |
| Abruptio placenta |
| Dysmorphic villi suggestive of developmental abnormality |
| Congenital infection |

| | |
|---|---|
| | Hydrops fetalis |
| Term and late preterm (34–42 weeks) | |
| | Fetal vascular malperfusion |
| | Feto-maternal hemorrhage |
| | Delayed villous maturation or placental maturation defect |

FIR: fetal inflammatory response