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REVIEW ARTICLE

Four major patterns of placental injury: a stepwise guide for understanding and implementing the 2016 Amsterdam consensus

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Abstract

The Amsterdam classification system defines four major patterns of placental injury, maternal vascular malperfusion, fetal vascular malperfusion, acute chorioamnionitis, and villitis of unknown etiology, and lists the histologic findings that characterize each. However, there continues to be uncertainty regarding specific definitions, histologic mimics, grading and staging, and what combination of findings is required to diagnose each pattern of injury in a reproducible fashion. The purpose of this review is to clarify some of these issues by suggesting a stepwise approach to more fully realize the potential of this new classification system. In our view, the critical steps for correctly identifying and communicating each pattern of injury are (1) familiarity with the underlying pathophysiology and known clinical associations, (2) incorporation of important gross findings, (3) learning to recognize underlying architectural alterations and defining features at low power, (4) using higher magnification to narrow the differential diagnosis and assess severity (grading) and duration (staging), and (5) adopting a template for generating standardized placental reports that succinctly provide useful information for patient care and research applications.

Introduction

Adult and pediatric surgical pathologists without specific perinatal training often struggle to make accurate and clinically relevant placental diagnoses. These issues largely relate to lack of familiarity with the clinical subject matter, the different nature of tissue reactions occurring in the placental environment, and a longstanding lack of rigor in defining diagnostic criteria and standardization of terminology. Short term problems range from missing important patterns of injury that may recur in subsequent pregnancies to wrong diagnoses leading to inappropriate clinical care. More globally, these problems have contributed to a failure to fully incorporate placental diagnoses into obstetric disease classification.

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This state of affairs was ultimately unsustainable and, thankfully, the recent Amsterdam consensus, convening expert perinatal pathologists from around the world for two important workshops, has brought clarity and standardization to the field. The first meeting held in Amsterdam in 2015 culminated in the eponymous Amsterdam classification that clearly defined the four major patterns of placental injury that will be the focus of this review [1]. The second meeting held in Dublin in 2018 resulted in the publication of a comprehensive textbook describing in more detail the entire range of placental pathology [2]. Other recent placental pathology textbooks supplement this consensus system, and it has now become the basis for all clinical and research activities in the field [3, 4].

Nevertheless, standardized terminology, written diagnostic criteria, and illustrations in textbooks can fall short of providing a practical diagnostic approach for the evaluation of individual specimens. The perinatal pathology service at UHCMC in collaboration with a group of interested clinicians over the past 30 years has developed a specific system for evaluating placentas that now incorporates all of the Amsterdam criteria. This review will focus on using this approach to reliably identify, characterize, and report the four processes that constitute the majority of clinically important placental pathology: maternal vascular malperfusion (MVM),

Table 1 Prevalence of the four major patterns of placental injury by gestational age in placentas submitted to pathology over a ten year period (2006–2015) at University Hospitals Cleveland Medical Center[a].

	Term (37–42 weeks)	Late preterm (32–37 weeks)	Early preterm (23–32 weeks)	Previable (<23 weeks)
N=	5311	1688	701	251
Maternal vascular malperfusion (MVM)	14.2[b]	17.4	22.7	4.0
Fetal vascular malperfusion (FVM)	11.4	8.0	6.3	2.4
Acute chorioamnionitis (ACA)	22.6	12.7	55.9	65.4
Villitis of unknown etiology (VUE)	7.3	5.1	1.6	0

[a]Unpublished data.

[b]Column percent positive.

fetal vascular malperfusion (FVM), acute chorioamnionitis (ACA), and chronic villitis (so-called "villitis of unknown etiology", VUE). For context, Table 1 provides a summary of the prevalence by gestational age (GA) for each of the four patterns amongst placentas examined at our institution (unpublished data). As can be seen, VUE and FVM are most common in term and late preterm placentas, MVM is most common in early and late preterm placentas, and ACA is most common in early preterm and previable gestations.

In brief, we take a four step approach. First, we consider the underlying biology, key elements of the clinical history, and the most salient aspects of the gross examination to establish the likely diagnostic possibilities before examining any slides. Second, we identify the dominant pattern(s) of injury by inspecting sections at low magnification. Third, we confirm, grade, and stage the primary pattern(s), identify additional lesions, and avoid pitfalls by focusing on specific areas at higher power. Fourth, we use a structured format to compose a final report that provides the necessary data for clinical interpretation and research applications in as succinct a fashion as possible.

General comments

Before discussing each of the patterns defined by the Amsterdam classification individually, a few general comments may be helpful. First, each pattern of injury has a spatially distinct cause and hence affects different regions of the placenta. MVM reflects compromised maternal blood flow and causes stereotypical changes in placental growth and distal villous morphology [5]. FVM represents obstructed fetal blood flow in the umbilical cord and is associated with alterations in chorionic and villous vessels [6]. ACA is elicited by amniotic fluid infection and results in an acute inflammatory response that is generally limited to contiguous structures; the membranes, chorionic plate and umbilical cord [7]. VUE is a maternal T-cell response to antigens in the fetal villous stroma and leads to inflammation centered on the distal villi [8]. Second, MVM and ACA are diffuse processes generally affecting all of the relevant placental structures, while FVM and VUE are more localized leading to focal or patchy changes. One should be reluctant to make a diagnosis of focal MVM or ACA or diffuse VUE or FVM before carefully considering alternative diagnoses and pitfalls as discussed below. Third, placental vascular lesions (MVM and FVM) are inherently more difficult to reproducibly diagnose and grade than the inflammatory lesions (ACA and VUE). ACA and VUE represent infiltration of the placenta by exogenous leukocytes that can be objectively localized and quantitated. Changes consistent with MVM or FVM represent a continuum of adaptations affecting intrinsic placental structures and often require subjective judgements regarding clinical context, gross measurements, thresholds for diagnosis, and sufficient multiplicity of supportive histologic findings. Finally, careful attention to the reason(s) for placental submission to pathology is useful for shaping expectations [9]. Pathologic examination often helps to explain adverse outcomes such as intrauterine fetal demise (IUFD), fetal growth restriction (FGR), preterm birth (PTB), and fetal CNS injury. Placentas submitted for abnormal maternal history, obstetric risk factors, prior adverse pregnancy outcomes, fetal congenital anomalies, and intrapartum monitoring abnormalities are much less likely to show any significant lesions; particularly in the context of term delivery, normal fetal and placental weights, and normal Apgar scores. One should never be reluctant to describe a placenta as having no significant diagnostic abnormalities.

The placental report

As alluded to above, clinical context is essential. Our past approach was largely passive. We have and continue to utilize a "placenta record" form, developed in collaboration with clinicians, that is submitted with all specimens. This form includes the following data: best estimate of gestational age (GA), OB index (full term deliveries, preterm deliveries, pregnancies ending prior to 20 weeks, and living children), relevant maternal history, baby weight, Apgar scores, and the

reason why the placenta was sent to Pathology. We have now adopted a more active approach. In addition to the placenta record, we now receive the complete maternal admitting history for all placentas. Prior to looking at any slides, we review this history, supplementing if necessary with additional data from the EMR, and synthesize our own short list of relevant diagnoses that is added to the clinical history field of the placenta record form that accompanies each final pathology report. While this process may seem involved, with practice it can be accomplished in only a few minutes.

Detailed placenta reports are of little use without timely reporting. A common mode of placental evaluation in the past has been to batch placentas to be signed out after all of the so-called more critical specimens are completed or when a subspecialty expert becomes available. This approach can no longer be justified. Some placental diagnoses identify immediately treatable diseases and are critical for the initiation of appropriate clinical care. Even in the absence of such actionable diagnoses, clinicians want to know in real time if there are placental findings that may help explain clinical abnormalities and alter the subsequent care plan for mother or baby. At our institution we aim to have final placental diagnoses in the EMR by 2–3 days after delivery during the week and 4–5 days following weekends.

With regard to the specific format of the placental report itself, we use three types of line diagnoses (Table 2). The first line sets the stage, providing the relative maturity of the villi for GA (expected: immature for less than 32 week pattern, slightly immature for 32–37 week pattern, and mature for >37 week pattern), placental weight with mention if below 10th, 5th or 3rd percentiles or greater than 90th, 95th or 97th percentiles for GA [3, 10], and important other general descriptors such as color, shape, or fragmentation. The second line diagnosis (or set of line diagnoses) states the major pattern or patterns of injury together with a complete list of the supportive findings plus any staging and/or grading parameters as appropriate. The third set of line diagnoses lists isolated findings not fully diagnostic for one of the four patterns plus any additional gross or microscopic abnormalities. We do not generally provide microscopic descriptions or additional comments, relying instead on the clarity of the Amsterdam system, our continuing medical educational efforts with the clinical departments, and direct interactions with the submitting physicians to communicate the import of specific diagnoses.

Maternal vascular malperfusion

Biology and clinical insights

Most recent evidence supports the theory that MVM develops due to a failure of the host to provide the necessary differentiation signals for fetal extravillous trophoblast to adequately invade the uterus and remodel the spiral arteries [11, 12]. These host deficiencies are believed to involve a combination of endometrial stromal (decidual), endothelial, and natural killer cell dysfunction, but primary trophoblastic defects could also play a role in some cases. Failure to adequately remodel the spiral arteries leads to abnormal perfusion of the intervillous space causing oxidative stress that results in reduced villous growth, accelerated villous maturation, and, in some cases, an increased release of anti-angiogenic mediators, such as soluble VEGF-1 receptor (sflt-1), into the maternal circulation [13–16]. These mediators can cause maternal endothelial damage, sometimes triggering the common pregnancy complication known as preeclampsia (PET). Importantly, release of these mediators is a consequence, not the underlying cause, of MVM. It follows that many placentas with MVM, often presenting with FGR, are not associated with PET. Conversely, many cases with PET do not show MVM. Explanations for PET in these cases include an enlarged placenta with excessive trophoblast resulting in an increased total level of anti-angiogenic mediators or a mother with an increased susceptibility to the effects of normal levels.

On a practical level, the combination of PET and FGR has the highest positive predictive value for MVM [17]. Preterm PET, type 1 pregestational diabetes, chronic renal disease, active maternal connective tissue disease, and nonhypertensive FGR with one or more of the following features, low early PAPP-A (pregnancy associated plasma protein A), oligohydramnios, decreased biophysical profile score, abnormal umbilical or uterine pulsed flow Doppler studies are also strong risk factors [18–22]. It is important not to over diagnose MVM based on the presence of weaker risk factors such as PET near term without severe features, chronic hypertension, obstructive sleep apnea, polycystic ovarian syndrome, maternal obesity, or gestational diabetes [9]. In addition, a diagnosis of MVM is unlikely in cases where the birthweight is greater than the 50th percentile for gestational age unless the pregnancy is complicated by diabetes, morbid obesity, or excessive pregnancy weight gain. Adverse outcomes associated with MVM, in addition to FGR, include indicated PTB, IUFD, abruptio placenta, and an increased risk for future cardiovascular disease in both the mother and child [23–27].

Gross pathologic clues

Three gross findings elevate the likelihood of MVM: (1) decreased placental weight for GA (usually less than the 10th percentile, but almost always less than the 50th percentile), (2) increased fetoplacental weight ratio for GA (placental weight reduced to a greater degree than fetal weight), and (3) villous infarcts (firm, well circumscribed

Table 2 Template for placental report and representative examples.

First line: Color shape, maturity, weight for GA	Abnormal color: Green-stained Brown-stained Yellow-stained	Completeness/ shape: Fragmented/?incomplete Bilobate	Maturity for GA: Immature (<32 weeks pattern at <37 weeks) Slightly immature (32–37 weeks pattern, any GA) Mature (>37 week pattern at >32 weeks) Histologically immature (immature pattern at >37 weeks) Histologically mature (mature pattern at <32 weeks)	Trimmed weight for GA (gm): Relatively small for GA (<3rd, 5th, or 10th percentile) Relatively large for GA (>90th, 95th, or 97th percentile for GA)
Second line: Major patterns of injury and supporting findings	MVM: Findings c/w MVM: ± Infarcts; AVM; DV[a] hypoplasia; arteriopathy; thin UC; superficial IS	FVM: Findings c/w FVM: ± thrombi; SV Intramural fibrin, obliteration, ectasia; AV (small, large), VSK	ACA: Acute chorioamnionitis, ± severe/ necrotizing, UC venous, arterial and/or chorionic vessel inflammation, severe fetal inflammatory response (grade 2) (Maternal stage; Fetal stage)	VUE: Chronic villitis, low/high grade, focal/multifocal/ patchy/diffuse with + perivillous fibrin, SV obliteration, AV
Additional lines: Other findings (examples)	Accessory lobe	Villous chorangiosis	Recent marginal retroplacental hematoma	Focally increased syncytial knots

Examples of placental reports:

– Mature, green-stained, bilobate placenta (410 G).

– Focally increased syncytial knots.

– Pigment laden macrophages in membranes.

– Relatively small, histologically mature placenta (240 G; < 5th percentile for 35 weeks gestational age).

– Findings consistent with maternal vascular malperfusion: distal villous hypoplasia, decidual arteriopathy: acute atherosis).

– Chronic villitis, high grade, patchy.

– Imature placenta (190 G).

– Acute chorioamnionitis with fetal inflammatory response in chorionic vessels (maternal stage 2; fetal stage 1).

– Recent marginal retroplacental hematoma.

[a]Additional abbreviations: *DV* distal villous, *SV* stem villous, *IS* implantation site.

wedge-shaped lesions based on the basal plate with a granular texture). However, there are a few caveats. First, while it is uncommon to have MVM without a small placenta, most small placentas are not associated with MVM, especially if the fetoplacental weight ratio is normal or decreased. Second, placental weight, like birthweight, may be in the normal range with maternal diabetes and other conditions that increase fetoplacental growth. Third, while isolated infarcts do sometimes occur in the absence of MVM, many gross lesions that appear to be infarcts by gross examination are revealed to be perivillous fibrin plaques (described below) after histological examination. Additional less specific placental gross findings sometimes seen with MVM include thin umbilical cord (<8 mm maximum diameter), peripheral insertion of umbilical cord, irregular placental contour, decreased width relative to length, and marginal atrophy.

Low power pattern

Accelerated villous maturation (AVM) is the defining feature of MVM. As originally conceived, this term described the situation where villi in a premature placenta resembled those from a term placenta. However, AVM also applies to term placentas. The cardinal finding in AVM is an alternating pattern of villous paucity and crowding (Fig. 1A). This pattern is apparent in a well- oriented full-thickness section, even before putting the slide on the microscope stage. However, this alternating pattern is not specific for AVM. The key additional findings for a diagnosis of AVM are (1) that the crowded areas show foci, often adjacent to stem villi, that are "fixed in place" by large dense syncytial knots, intervillous fibrin, and villous agglutination (Fig. 1B) and (2) that the villi within the areas of paucity are extremely small on cross section and show a lack of branching on longitudinal section (Fig. 1C). When paucity exceeds 30% of the total volume in the lower and inner 2/3 of the villous parenchyma, the term distal villous hypoplasia, rather than AVM, is used indicating MVM of longer duration and increased severity (Fig. 1D). When villous crowding and/or increased syncytial knots occur in the absence of paucity a separate diagnosis of focally increased syncytial knots can be made, but this is not sufficient to establish a diagnosis of MVM

Villous infarction and infarction-hematoma are additional features of MVM that further substantiate the diagnosis and indicate greater severity. A villous infarct is a sharply circumscribed solid lesion characterized histologically by contiguous degenerating villi showing collapse of the intervillous space with intervening fibrin and karyorrhectic debris, loss of villous trophoblast basophilia, and degenerative changes in the villous stroma with persistence of capillaries (Fig. 1E). Even small foci with this pattern are diagnosed as infarcts as they most likely represent the edges of larger lesions. An infarction-hematoma (also known as rounded intraplacental hematoma) is a centrally hemorrhagic villous infarct [28, 29]. It is differentiated from an intervillous thrombus by virtue of a surrounding layer of infarcted villi at least 4–5 villi in diameter (Fig. 1F). Some consider infarction-hematoma to be an "intraplacental" form of abruptio placenta and these lesions have been associated with more severe adverse outcomes than simple infarcts alone [29].

Subclassification, grading, and staging

There is no consensus grading system for MVM. We have recently published a provisional grading system in which high grade MVM was defined by AVM plus one or more of the following features: placental weight <3rd percentile for GA, multiple villous infarcts, and distal villous hypoplasia [9]. Others have employed a point scoring system, primarily for research applications [30]. Two additional histologic findings that support, but do not by themselves establish a diagnosis of MVM are decidual arteriopathy and a superficial implantation site. Subtypes of decidual arteriopathy—usually seen in the membrane roll - include mural hypertrophy (Fig. 1G) and fibrinoid necrosis with or without acute atherosis (Fig. 1H, I). A superficial implantation site is defined by abundant decidua basalis containing extravillous trophoblast giant cells and/or persistent muscularization (lack of physiologic change) in basal plate arteries. The most salient features of MVM are summarized in Table 3.

Differential diagnosis and pitfalls

Villous dysmaturation is a related lesion where focally increased syncytial knots occur in a background of delayed villous maturation [1]. This pattern is most common in diabetic mothers (Fig. 1J). Dysmorphic villi, seen in some genetic and chromosomal abnormalities [31], can have increased syncytial knots and reduced branching, but also show one or more additional features such as disproportionally large edematous stem villi, abnormal villous contour, trophoblast inclusions, abnormal villous blood vessels, or syncytial sprouts (Fig. 1K). General villous undergrowth, sometimes seen in the placentas of infants with nonhypertensive IUGR, can mimic distal villous hypoplasia, but lacks the long thin unbranched villi, syncytial knots, intervillous fibrin, and villous agglutination required for a diagnosis of MVM.

One common pitfall is to confuse a perivillous fibrin plaque with a villous infarct. Perivillous fibrin plaques are less well circumscribed, show greater separation between villi, and lack degenerative changes such as loss of basophilia and karyorrhectic debris (Fig. 1L) [32]. These lesions

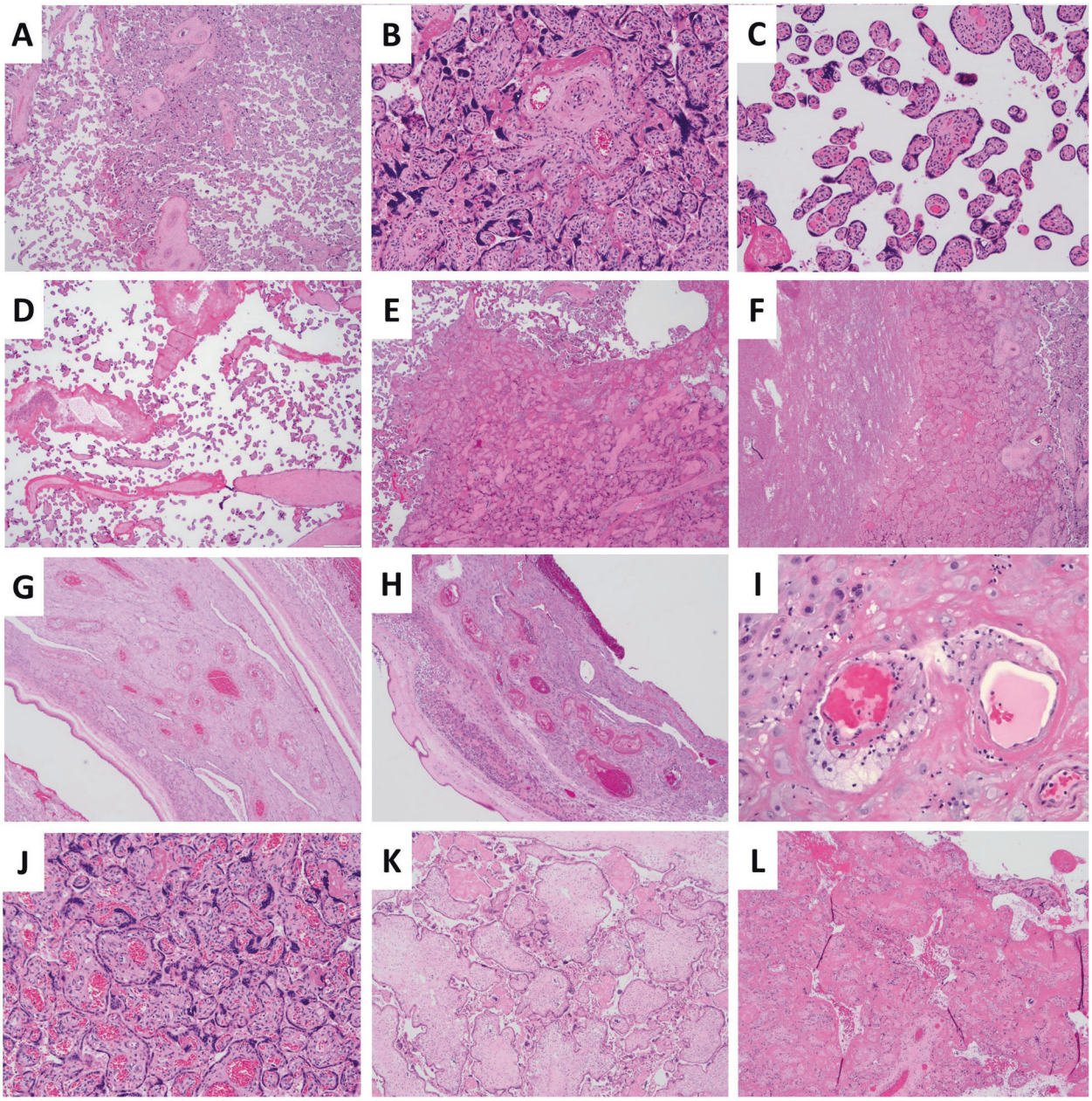

Fig. 1 Findings consistent with maternal vascular malperfusion (MVM) and potential mimics. A Accelerated villous maturation shows alternating areas of villous crowding with agglutination and syncytial knots (center) flanked by areas with decreased density and branching of terminal villi (H&E 20×). **B** Crowded area in accelerated villous maturation showing large confluent syncytial knots, agglutination, and foci of intervillous fibrin in an area adjacent to a fetal stem villus (H&E 100×). **C** Area of paucity in accelerated villous maturation with scant, small terminal villi intermixed with mature intermediate villi (H&E 100×). **D** Distal villous hypoplasia composed entirely of areas of paucity composed of thin villi with reduced branching (i.e. lacking the crowded component) filling the entire space between large fetal stem villi (H&E 20×). **E** Villous infarct with sharply circumscribed outline, collapse of the intervillous space, intervillous fibrin, karyorrhectic debris, degenerating neutrophils, and loss of trophoblastic and villous stromal basophilia (H&E 20×). **F** Infarction-hematoma is a basally oriented lesion showing typical peripheral infarction surrounding a rounded, intervillous hematoma (H&E 20×). **G** Decidual arteriopathy, mural hypertrophy, is defined by arteriolar enlargement, thickening of the muscular wall, and reduction of the lumen to <30% of the vessel diameter (H&E 40×). **H** Decidual arteriopathy, fibrinoid necrosis, is defined by arteriolar enlargement and replacement of the muscular wall by bright-red, "glassy" fibrinoid material (H&E 40×). **I** Decidual arteriopathy, acute atherosis, is a more severe stage of fibrinoid necrosis that includes foamy lipid-laden macrophages embedded within the vessel wall (H&E 200×). **J** Villous dysmaturation is characterized by histologically immature villi (increased stroma) surrounded by focally increased syncytial knots (H&E 100×). **K** Dysmorphic villi are abnormal villi (edematous with irregular contour) surrounded by focally increased syncytial knots (H&E 40×). **L** Perivillous fibrin plaque is a solid lesion mimicking a villous infarct, but with a more irregular contour, preservation of space between villi, and a lack of ischemic changes such as loss of basophilia and necrotic debris in the intervillous space (H&E 40×).

Table 3 Maternal vascular malperfusion (MVM): summary.

Defining features
Accelerated villous maturation or distal villous hypoplasia
Associated findings
Decreased placental weight/ increased fetoplacental weight ratio for GA
Villous infarcts/ Infarction-hematomas
Decidual arteriopathy: mural hypertrophy, fibrinoid necrosis, acute atherosis
Thin umbilical cord (<8 mm maximum diameter)
Superficial implantation site: muscularized basal plate arteries, basal plate trophoblast giant cells
High grade (provisional)
MVM with placental weight < 3rd percentile for GA, multiple infarcts or distal villous hypoplasia
Differential diagnosis/pitfalls
Focally increased syncytial knots (alone)
Villous dysmaturity
Dysmorphic villi
Perivillous fibrin plaque (localized perivillous fibrin deposition)
Massive perivillous fibrin deposition ("maternal floor infarction")

are of minimal clinical significance, and are not considered to be part of the spectrum of MVM. However, when the histologic pattern associated with a localized perivillous plaque becomes confluent, occupying at least 30% of one full-thickness slide and the lesion involves at least 30% of the placental parenchyma, a diagnosis of massive perivillous fibrin deposition (also known as "maternal floor infarction") should be made [33–35]. This diffuse pattern is important to recognize because of its high recurrence rate and association with adverse outcomes. In general, an isolated finding of patchy or diffuse perivillous fibrin that falls below the 30% threshold is considered clinically insignificant and is not mentioned.

Reporting

In cases of MVM, we use the header "findings consistent with MVM" followed by all supporting findings. The minimum criterion for diagnosis is AVM. Other features commonly listed include villous infarcts or infarction-hematomas, distal villous hypoplasia, decidual arteriopathy, thin umbilical cord, and superficial implantation site. Some features that are part of the spectrum of MVM, such as focally increased syncytial knots, villous infarcts, and decidual arteriopathy, should be added as separate line diagnoses when identified in the absence of other findings consistent with MVM. Others, such as superficial implantation site and thin umbilical cord are less well defined and/or less specific and should be considered as supportive but not as distinct "stand alone" diagnoses.

Fetal vascular malperfusion (FVM)

Biology and clinical insights

FVM is most strongly associated with chronic or partial intermittent umbilical cord occlusion [36–39]. Less common risk factors include maternal diabetes, antiphospholipid antibody syndrome, or antiplatelet antibodies and fetal cardiac anomalies, polycythemia, or thrombophilic mutations [40–44]. All of these associations are consistent with Virchow's triad of conditions predisposing to thrombosis (stasis, hypercoagulability, and endothelial activation) and combinations of risk factors may apply in individual cases. The most common sequence is for obstructed umbilical blood flow to cause increased intraplacental venous pressure and circulatory stasis. The increased pressure results in structural changes in large placental veins and circulatory stasis leading to loss of blood vessels in small clusters of the most poorly perfused distal terminal villi (global pattern of FVM). Continuing stasis and/or thrombophilia promotes the formation of occlusive thrombi in large chorionic or stem villous vessels resulting in complete loss of perfusion and involutional changes affecting large segments of the downstream distal villous tree (segmental pattern of FVM). It follows that global FVM is often a precursor for segmental FVM and that features of both can occur in the same placenta. Less commonly, thrombi form without apparent stasis-related changes and the pattern is entirely segmental.

Antenatal findings associated with FVM include decreased fetal movement, category 3 fetal heart rate decelerations, and prolonged meconium exposure. Neonatal complications include end-organ thrombi, decreased platelets, and abnormal neurologic status. Associated adverse outcomes include IUFD, neonatal encephalopathy, fetal stroke, cerebral palsy, and mild FGR [38, 45–47]. FVM is generally not a cause of preterm birth or recurrent reproductive loss.

Gross pathologic clues

The most common gross correlate of FVM is an umbilical cord (UC) at risk. Potentially obstructive pathologic conditions include hypercoiling (>3 coils/10 cm), excessive length (>70 cm), marginal/ membranous or furcate insertion site, tethering by an amnionic web, and decreased Wharton's jelly/ thin UC (< 8 mm diameter). A clinical history of umbilical cord entanglements (tight nuchal or body cord, true knot) is also relevant. Unlike MVM, which is associated with a small fetus, a very small placenta, and an elevated fetoplacental weight ratio, FVM is more commonly associated with a low-normal birthweight, a normal to large placenta, and a reduced fetoplacental weight ratio [9]. Relative elevations in placental weight are most likely

the consequence of chronic congestion due to decreased umbilical venous return. Reference tables listing percentiles for weight and fetoplacental weight ratio relative to GA are available in several placental textbooks [3, 10]. Rare gross findings in FVM include thrombosis of umbilical or chorionic plate vessels or a segmental area of pale-firm consolidated parenchyma.

Low power pattern

Multiple foci of avascular villi (AV) or villi with stromal vascular karyorrhexis (VSK) are the defining features of FVM. These findings are usually accompanied by either an umbilical cord at risk or additional lesions involving large muscularized fetal vessels in the stem villi or chorionic plate. Four large vessel lesions are recognized in the Amsterdam classification. The first two, luminal thrombi (Fig. 2A) and stem vessel obliteration (Fig. 2B, C), are more common in the segmental pattern of FVM. The second two, intramural fibrin deposition and venous ectasia (lumen >4× larger than nearest adjacent vessel) are more common with the global pattern of FVM (Fig. 2D). The distinction between intramural fibrin that extends to the luminal surface and a luminal thrombus that has been incorporated into the vessel wall can be arbitrary. The general rule is to diagnose thrombi only when the lesion protrudes into or partially occludes the vascular lumen. AV are clusters of mature villi with hyalinized villous stroma, intact trophoblast, and a complete absence of capillaries. They are clearly distinct from surrounding normal villi and generally lack any surrounding fibrin. Small foci (2–4 villi) are most commonly seen near the basal plate (Fig. 2E). Small foci alone are consistent with global FVM. Large (>15) foci may be located anywhere in the parenchyma (Fig. 2F). Any focus of large AV indicates segmental FVM. Intermediate sized (5–15) foci are less specific and can accompany either global or segmental FVM, depending on other findings. VSK is an early stage preceding AV. Foci suggestive of VSK stand out at low power based on increased cellularity, edema, and a "smudgy-looking" stroma (Fig. 2G). VSK is confirmed at higher magnification by finding karyorrhectic cellular debris derived from stromal fibroblasts, endothelial cells, and/or circulating nucleated cells (Fig. 2H). Patchy villous edema or even delayed villous maturation, possibly reflecting increased hydrostatic pressure, is common with FVM, but not specific. Hypovascular villi are not a recognized diagnostic feature of FVM.

Subclassification, grading, and staging

Minimal criteria for FVM in our practice are two or more intermediate to large foci of AV/VSK or three or more foci of small-intermediate sized AV/VSK. For exclusively small foci of AV/VSK we also require either an umbilical cord at risk or large fetal vessel lesions. High grade FVM is defined by either a total number of affected villi exceeding 15/slide (total AV/VSK divided by the number of parenchymal slides) or two or more fetal thrombi. No formal staging system exists, but as described above, the global FVM pattern generally precedes segmental FVM and foci of VSK are thought to progress with time to AV. The most salient features of FVM are summarized in Table 4.

Differential diagnosis and pitfalls

The differential diagnosis of FVM includes two major processes; IUFD with involutional fetal vascular changes and VUE with stem vessel obliteration and extensive AV. FVM can be a cause of IUFD, so distinguishing FVM from secondary involutional changes is especially important. In a sense the changes seen in the placentas of IUFD are a type of FVM; diffuse and global following the death of the fetus. However, the large vessels and villi in IUFD without preceding FVM show patchy-diffuse changes (stem vessel obliteration and AV/VSK) in all sections with a gradual transition between more or less affected areas. Features that suggest preexisiting FVM in an IUFD include (1) UC abnormalities and/or specific large vessel changes (ectasia, intramural fibrin, thrombi) and (2) sharply circumscribed foci of AV/VSK, clearly divergent from surrounding villi in their stage of involution. VUE, usually high grade, can be complicated by inflammation-related obliteration of stem vessels with large areas of downstream AV or VSK (see below). FVM is excluded when any of the adjacent villi show a lymphocytic infiltrate and should be diagnosed with caution when VUE is identified in any of the slides. Another distinguishing feature is that AV or VSK in VUE are often accompanied by perivillous fibrin.

Pitfalls leading to a false positive diagnosis of FVM include myxoid intimal cushions without intramural fibrin, degenerating AV surrounded by fibrin, isolated sclerotic immature AV, and foci of intervillous fibrin that have become re-epithelialized by syncytiotrophoblast. Myxoid intimal cushions are normal findings in some large fetal stem vessels (Fig. 2I) [48]. Only those with clear-cut, laminated, or occasionally calcified, intramural fibrin deposits are pathologic. Small-intermediate sized foci of avascular villi lacking a viable trophoblastic layer and surrounded by a thin layer of perivillous fibrin are degenerative, rather than ischemic, in nature (Fig. 2J). Likewise, occasional isolated immature sclerotic villi that appear to be remnants from a much earlier stage of pregnancy are common, especially in preterm placentas (Fig. 2K). They are also degenerative in nature. Finally, nodular foci of intervillous fibrin can become surrounded by an attenuated layer of syncytiotrophoblast and lose their eosinophilia leading to the false impression of hyalinized stroma (Fig. 2L). Careful examination usually distinguishes such changes from a true stromal reaction.

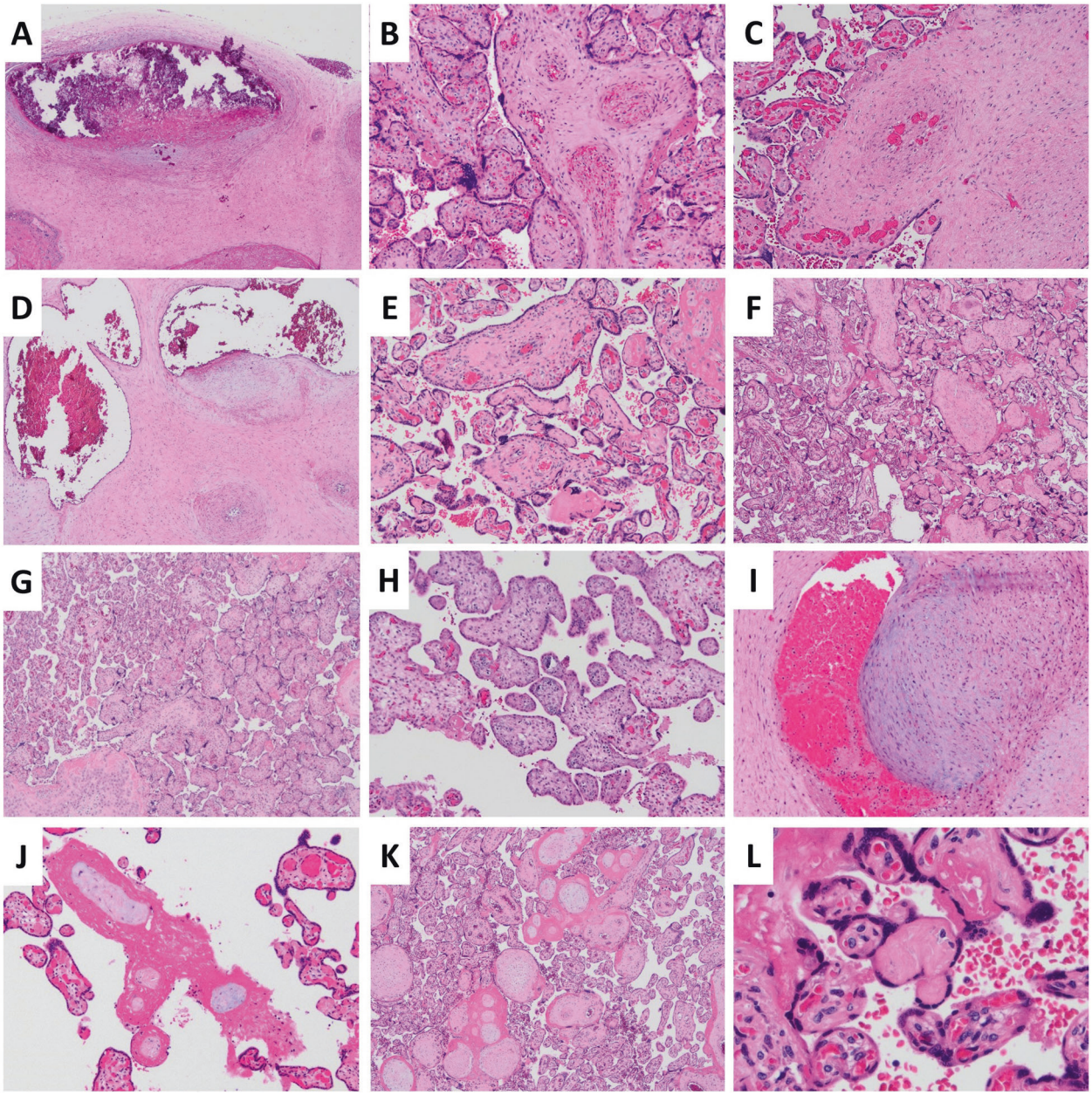

Fig. 2 Findings consistent with fetal vascular malperfusion (FVM) and potential mimics. A Occlusive chorionic vessel thrombus with a mixture of remote and more recent fibrin showing focal mineralization consistent with prolonged duration (H&E 40×). **B** Fetal stem vessel obliteration, early stage, with a mixture of loose connective tissue and entrapped RBC occluding the lumen of stem vessels (H&E 100×). **C** Fetal stem vessel obliteration, later stage, with stem vessels occluded by dense fibrous connective tissue and a few small secondary lumina, possibly representing recanalization (H&E 100×). **D** Venous ectasia and intramural fibrin deposition showing marked dilatation of stem villous veins relative to adjacent arteries (lower right) and laminated fibrin embedded in subendothelial loose fibrous connective tissue in the vessel wall (H&E 40×). **E** Small focus of contiguous avascular villi with stromal hyalinization and an intact normal trophoblast layer (H&E 100×). **F** Large focus of contiguous avascular villi with stromal hyalinization involving both stem and terminal villi (H&E 40×). **G** Villous stromal vascular karyorrhexis (VSK) with enlarged, edematous branching villi (center) showing "smudgy" stromal-vascular alterations at scanning magnification (H&E 40×). **H** VSK at higher magnification showing reduced vascularity, "dusty" mineralization, and karyorrhectic cellular debris in the villous stroma and capillary lumens (H&E 200×). **I** Normal subendothelial myxoid "cushion", eccentric loose fibrous connective tissue without fibrin deposition is a normal finding seen in occasional large fetal vessels (H&E, 100×). **J** Degenerating villi surrounded by fibrin without trophoblast are a common feature in many mature placentas (H&E 100×). **K** Large avascular immature intermediate villi with pale fibrotic cores are a common finding, especially in preterm placentas (H&E 40×). **L** Re-epithlialized perivillous fibrin is a reactive-reparative process that can mimic a villus without vessels (H&E 400×).

Table 4 Fetal vascular malperfusion (FVM): summary.

Primary defining features
Global pattern: Exclusively small-intermediate sized foci of avascular villi/ villous stromal vascular karyorrhexis
Segmental pattern: Large foci of avascular villi/ villous stromal vascular karyorrhexis
Secondary defining features
Umbilical cord at risk for compression
Pathologic: hypercoiled, long (>70 cm), marginal/membranous/ furcate insertion, tight amnion web
Clinical: entanglements (nuchal, body), true knot
Large fetal vessel lesions
Global pattern: Intramural fibrin and/or venous ectasia, fetal stem vessels
Segmental pattern: Fetal large vessel thrombi and/or stem villous vascular obliteration
High grade
FVM with multiple large vessel thrombi or an overall average of >15 affected villi/ slide
Differential diagnosis/ pitfalls
Involutional changes of IUFD
VUE with large foci of avascular villi
Degenerating villi surrounded by fibrin
Intervillous fibrin re-epithelialized by villous trophoblast

Reporting

In cases of FVM, we use the header "findings consistent with FVM" followed by all of the supporting findings. The decision as to when to use this header is somewhat subjective, but we generally require an umbilical cord at risk or at least one large fetal vessel lesion in combination with AV or VSK. As explained above, FVM has global and segmental subtypes. However, these patterns often overlap and we do not explicitly distinguish them in our diagnostic reports. As previously discussed for MVM, isolated findings that we consider to be consistent with but not diagnostic of FVM receive separate line diagnoses. These include scattered small foci of AV/VSK, a single intermediate-large focus of AV/VSK, an umbilical cord at risk, and isolated large fetal vessel lesions. Venous ectasia is not reported in the absence of other lesions.

Acute chorioamnionitis

Biology and clinical insights

The gravid uterus, owing to the need to protect fetal development and prevent rejection of the allogeneic fetus, is poorly equipped to effectively control bacterial and fungal infections that breach the normal anatomic barriers provided by the cervix and intact placental membranes [49, 50]. Of the three arms of the immune system, two - adaptive immunity and complement activation - are actively down regulated in the placenta, leaving only neutrophil-predominant innate immunity to defend the fetus from ascending infection [51]. This neutrophilic response defines the lesion known as histologic acute chorioamnionitis (ACA). In ACA, maternal neutrophils exit from decidual venules and migrate into the chorion and amnion in response to microbial chemotactic factors in the amniotic fluid (maternal inflammatory response/ MIR). Later, fetal neutrophils join the response by migrating across large vessel walls in the chorionic plate and umbilical cord (fetal inflammatory response/ FIR). The MIR in ACA can sometimes trigger the labor cascade leading to premature delivery [52]. The FIR may occasionally lead to over-activation of the fetal immune system with detrimental effects on fetal organs including the CNS, lungs, and intestinal tract [53–56].

Some recent authors have argued that ACA, especially at term, is often not infectious [57]. This contradicts older studies showing that organisms can be cultured in the great majority of placentas at all GA with histologic ACA [58–61]. Contributing to this confusion are the following: (1) the early stages of histologic ACA are less specific than later stages and occasionally reflect other processes, (2) most histologic ACA is clinically silent, and (3) many diagnoses of clinically suspected ACA are false positives with no evidence of histologic ACA or organisms in the placenta [62]. A new study has reconfirmed the infectious etiology of ACA and demonstrated that the bacterial load as determined by PCR is directly proportional to the stage of the MIR (see below) as determined by Amsterdam criteria [63]. Clinical factors that increase the prior probability of finding ACA in the placenta include preterm or prolonged rupture of membranes, marginal abruption, cervical insufficiency, prior history of late miscarriage or early preterm delivery, and low Apgar scores [9].

A diagnosis of histologic ACA with appropriate grading and staging has significant clinical value. Benefits include: (1) delineating a distinct subgroup of spontaneous preterm deliveries, (2) helping to guide antibiotic usage and time of discharge for both mother and infant, (3) identifying subtypes of infection caused by candida and listeria that require special management, and (4) recognizing specific risk factors for adverse outcomes such as umbilical arteritis (FIR stage 2), associated with increased levels of circulating fetal cytokines, and high grade FIR, associated with adverse neurologic outcomes [64–70].

Gross pathologic clues

Gross examination plays a limited role in the diagnosis and categorization of ACA. The amnion overlying the chorionic

plate may be dull gray and cloudy, or even green (purulent), and there can be a haziness emanating from the major chorionic vessels reflecting the FIR. Umbilical cord cross section may show gray-white arcs around the vessels (fetal stage 3, see below) and the external surface of the cord can have yellow plaques suggestive of candida infection [69, 70]. Rarely, the cut surface of the parenchyma may show geographic areas of abscess formation suggestive of listeria infection [68]. However, all of these features are more readily and specifically identified by histology.

Low power pattern

The defining feature of ACA is a patchy-diffuse neutrophilic infiltration of the subchorionic fibrin, first seen in the thinner areas of the chorionic plate (acute subchorionitis, Fig. 3A). Any diagnosis of ACA without subchorionitis should be suspect. One of the major changes introduced by the Amsterdam system is the additional requirement that inflammation is also present, at least focally, in the amnion and/or chorion. Isolated acute subchorionitis, is now considered less specific for infection and is reported as a separate diagnosis. Thorough examination of sections from the chorionic plate, membrane rolls and umbilical cord specifies the stage and grade of ACA as detailed below. Low power findings of special significance include UC peripheral abscesses in candida infection, acute intervillositis with abscesses in listeria infection, a mixed histiocytic-neutrophilic infiltrate in cases of chronic (subacute) mycoplasma infection, and foci of acute villitis or intervillositis, suggestive of fetal or maternal sepsis, respectively [50, 71].

Subclassification, grading, and staging

Grading indicates the severity of the maternal and fetal inflammatory responses while staging reflects their duration. The grading systems are each binary. A high grade MIR is defined by the finding of subchorionic abscesses (>30 cells in minimum diameter) or a diffuse band-like neutrophilic infiltrate between amnion and chorion (>15 cells in minimum diameter). No clinical utility for distinguishing high grade MIR has yet been reported. The more clinically relevant high grade FIR is defined by confluent neutrophils and evidence of vessel wall alterations (endothelial damage, myocyte disarray, or mural thrombi) in chorionic vessels on the side facing the amniotic cavity (Fig. 3B, C).

The staging systems each have three levels. Stage 1 MIR requires patchy-diffuse neutrophils in the membranous chorion, usually centered at the junction of decidua and chorion laevae trophoblast (Fig. 3D), stage 2 at least some neutrophils in the amnionic connective tissue, and stage 3 greater than 40% necrosis of amniocytes, basement membrane eosinophilia, and karyorrhexis of neutrophils (Fig. 3E). A stage 1 FIR is defined by neutrophils in the wall of the umbilical vein and/or chorionic vessels, stage 2 by neutrophils in the wall of one or both umbilical arteries (Fig. 3F), and stage 3 by the presence of neutrophils in Wharton's jelly, at least focally showing an arc-like distribution around one or more umbilical vessels (Fig. 3G). Importantly, the presence of scattered neutrophils in Wharton's jelly does not upstage the FIR to stage 3. The most salient features of ACA are summarized in Table 5.

Differential diagnosis and pitfalls

Prolonged meconium exposure can elicit some features seen in ACA including a stage 1 FIR and occasional neutrophils in the membranes, but generally lacks the patchy-diffuse subchorionitis typical of ACA [72]. ACA and meconium release often occur together, so it is important to report both processes when all of the criteria for ACA are fulfilled. Chronic (lymphocytic) chorioamnionitis and chorionic histiocytic hyperplasia are related lesions, sometimes associated with VUE [73, 74]. The former is defined by lymphocytes in the membranes (Fig. 3H); the latter by a band-like infiltrate of histiocytes in the lower portion of the chorionic plate (Fig. 3I). Both lack neutrophils. Eosinophilic/ T-cell fetal vasculitis is an idiopathic lesion, also occasionally associated with VUE, that must be distinguished from the FIR in ACA [75–77]. It is characterized by a focal mixed eosinophilic/ lymphocytic infiltrate in the wall of chorionic or stem villous vessels (Fig. 3J, K). Other features of ACA are absent, the polarization of the inflammatory infiltrate is random - often facing away from the amniotic cavity, and neutrophils are absent. It should not be confused with ACA showing a mixed eosinophilic-neutrophilic infiltrate, which can be seen in some early preterm births.

Pitfalls in the diagnosis of ACA include degenerative processes such as apoptosis of chorion laevae trophoblast (Fig. 3L) and ischemic necrosis of the decidua, sometimes misinterpreted as maternal stage 1 ACA, and apoptosis of vascular smooth muscle cells in the wall of the umbilical vein in stillbirths, sometimes misinterpreted as fetal stage 1 ACA (so-called "pseudovasculitis") [78]. Key distinctions include their focal nature, predominance of tissue necrosis over inflammation, and the lack of subchorionitis below the chorionic plate or neutrophils within the membranous chorion.

Reporting

Our approach to reporting ACA is to give a narrative description followed by the maternal and fetal stages in parentheses. We feel that these additional descriptive terms

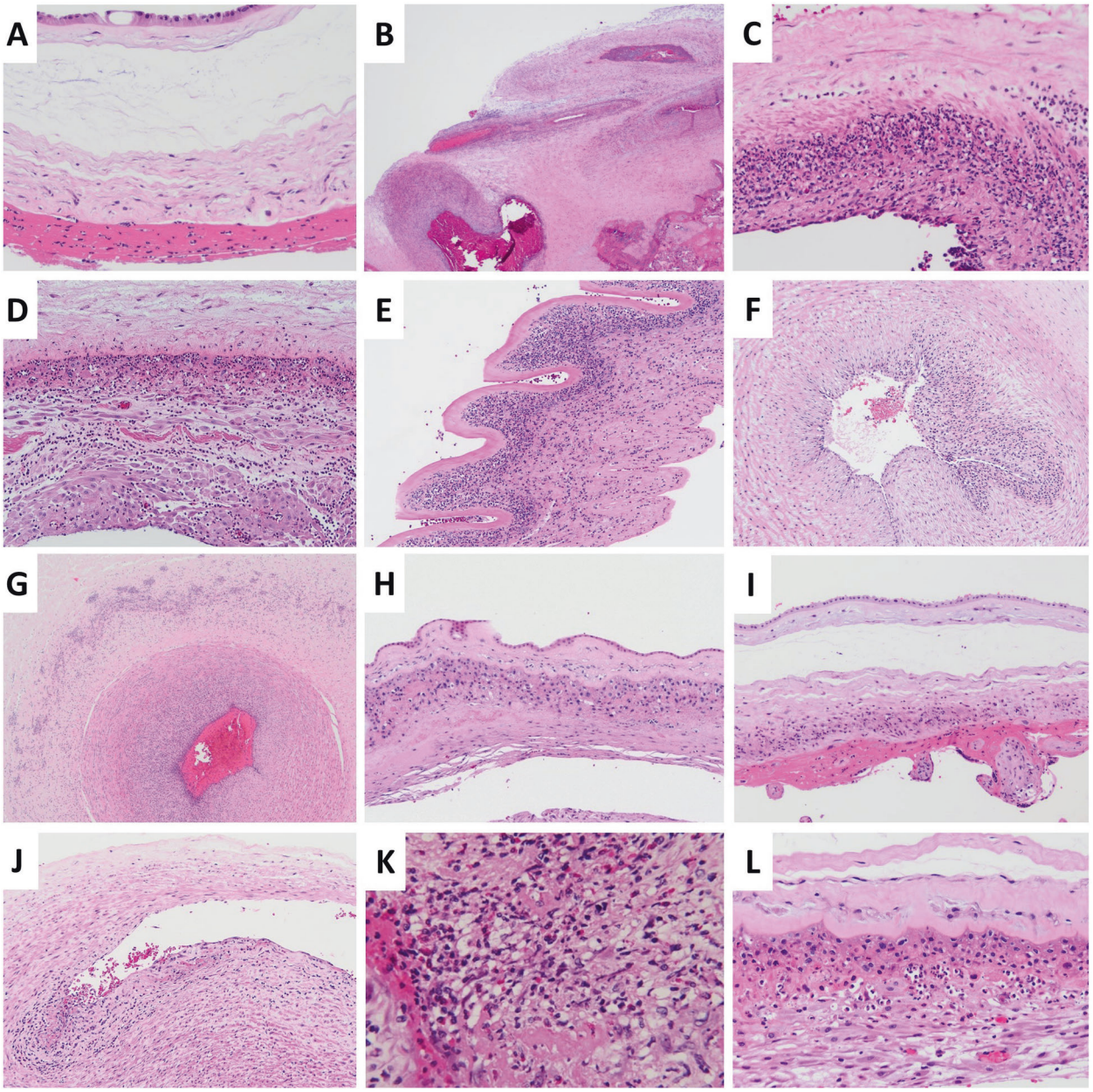

Fig. 3 Findings consistent with acute chorioamnionitis (ACA) and mimics. A Acute subchorionitis, neutrophils in subchorionic fibrin, is a necessary but not sufficient finding for the diagnosis of ACA (H&E 200×). **B** A high grade fetal inflammatory response (FIR) is usually obvious at scanning magnification as a dense cellular infiltrate in the chorionic vessels on the side facing the amniotic fluid (H&E 20×). **C** Higher power examination of high grade FIR reveals confluent neutrophils and endothelial cell alterations such as activation and focal dehiscence (H&E 400×). **D** Stage 1 maternal inflammatory response (MIR) most commonly presents as neutrophils in the membranous decidua piling up at the junction between the decidua and chorionic trophoblast with a few neutrophils in the overlying fibrous connective tissue (H&E 100×). **E** Necrotizing ACA (Stage 3 MIR) has three defining features; sloughage of amnionic epithelium, eosinophilia and thickening of the amnionic basement membrane, and karyorrhexis of neutrophils in the amnionic fibrous connective tissue (H&E 100×). **F** Umbilical arteritis (Stage 2 FIR) begins as an accumulation of neutrophils in the subintimal connective tissue of one or both umbilical arteries (H&E 100×). **G** Concentric umbilical perivasculitis (Stage 3 FIR) is defined by organized bands of degenerating neutrophils in Wharton's jelly surrounding one or more umbilical vessels (H&E 100×). **H** Chronic (lymphocytic) chorioamnionitis is defined as a patchy mild mononuclear cell infiltrate including at least some small (T) lymphocytes in the membranous amnion or chorion (H&E 100×). **I** Chorionic histiocytic hyperplasia is a band-like accumulation of activated macrophages located just above the subchorionic fibrin in the chorionic plate, most commonly seen in cases of chronic villitis (H&E 100×). **J** Eosinophilic/T-cell fetal vasculitis can mimic a stage 1 FIR in ACA at low magnification, but is usually oriented toward the intervillous space rather than the amniotic fluid, and lacks neutrophils (H&E 100×). **K** High power examination in Eosinophilic/T-cell fetal vasculitis reveals a mixed infiltrate of small lymphocytes and eosinophils (H&E 400×). **L** Apoptosis of chorionic trophoblast mimics degenerating maternal neutrophils in stage 1 ACA (H&E 200×).

Table 5 Acute chorioamnionitis (ACA): summary.

Defining feature
Acute subchorionitis **and** neutrophils in chorion and/or amnion
Maternal inflammatory response
Stage (duration): 1-chorionitis, 2-amnionitis, 3-amnion necrosis/ PMN fragmentation
High grade (severe): subchorionic microabscesses
Fetal inflammatory response
Stage (duration): 1-PMN umbilical vein/ chorionic vessel, 2-PMN umbilical artery, 3-concentric band/arc of PMN in Wharton's jelly
High grade (severe): confluent PMN with fetal vessel wall damage, chorionic vessels
Differential diagnosis/ pitfalls
Isolated acute subchorionitis (no chorioamnionitis) or fetal inflammatory response (no maternal inflammatory response)
Chronic (lymphocytic) chorioamnionitis
Chorionic histiocytic hyperplasia
Eosinophilic/ T-cell fetal vasculitis
Necrosis/ karyorrhexis of decidual stromal cells, chorion laevae trophoblast, or fetal vascular smooth muscle cells (in IUFD)

are helpful for clinicians who may not recall the details of the staging system. The following terms are used: severe ACA for maternal grade 2, severe FIR for fetal grade 2, necrotizing ACA for maternal stage 3, umbilical phlebitis and/or FIR in chorionic vessels for fetal stage 1, umbilical arteritis or panvasculitis for fetal stage 2, and umbilical perivasculitis or necrotizing funisitis for fetal stage 3. Special features of clinical significance such as severe grade 2 FIR or peripheral funisitis suggestive of candida are given separate line diagnoses. Isolated features that are part of the spectrum of ACA, but not by themselves diagnostic, are reported separately. These include isolated early acute subchorionitis and/or an isolated fetal inflammatory response involving chorionic or umbilical vessels.

Villitis of unknown etiology

Biology and clinical insights

Chronic villitis is a maternal T-cell mediated immune response to antigens in the fetal villous stroma [79, 80]. Congenital infections of the so-called TORCH-type are a relatively uncommon, but clinically important, cause of chronic villitis [81]. However, the majority of cases are idiopathic, hence the acronym "villitis of unknown etiology" or VUE. A considerable body of evidence indicates that this relatively common lesion (seen in 5–15% of all term placentas) is the consequence of circulating maternal T cell that cross into the villous stroma and are subsequently activated by transplantation antigens expressed on the surface of activated fetal antigen presenting cells (Hofbauer cells). This evidence includes a maternal serum chemokine signature similar to graft versus host disease, pathway analysis of RNA expression in microdissected villi with VUE showing the overexpression of genes related to allograft rejection and T-cell trafficking, upregulation of fetal class II MHC antigen expression, frequent fetal class II MHC mismatch with the mother, and an increased incidence of VUE in ovum donation pregnancies which lack any shared antigens with the mother [82–84]. In most cases alloreactivity is localized and of no consequence to the pregnancy. However, more extensive VUE is the second most common cause of FGR and a significant contributor to IUFD, cerebral palsy, and recurrent reproductive failure [67, 85–88]. Clinical conditions predisposing to VUE include artificial reproductive technology, especially the aforementioned ovum donation pregnancy, autoimmune disease, and antenatal substance abuse [8, 9]. An unusual association of maternal obesity with VUE involving female, but not male, infants has been reported and some evidence suggests that VUE is the major placental finding in a subset of cases of PET [89, 90]. Unlike MVM, FGR associated with VUE tends to have normal maternal and umbilical pulsed flow Doppler studies. Most importantly, VUE has a significant recurrence rate suggesting that maternal priming to fetal antigens causes increased risk in subsequently affected pregnancies [86, 87].

Gross pathologic clues

Like ACA, there are few gross clues suggesting VUE. Placentas may be small, usually with a normal fetoplacental weight ratio. In some severe cases areas of ill-defined, pale-firm parenchyma may be detected on cut section. Rarely, a partially necrotic, infarct-like mass may be seen.

Low power pattern

The defining feature of VUE is an asymmetric, haphazardly arranged, infiltrate of small lymphocytes in the villous stroma with evidence of secondary tissue damage such as fibrosis, edema, or vascular obliteration (Fig. 4A). Helpful findings on low power examination can be separated into three groups: (1) primary findings in affected villi, (2) secondary changes in proximity to affected villi, and (3) associated lesions in other locations. Foci of VUE are generally paler and more basophilic than the surrounding parenchyma and often adhere to one another (Fig. 4B). They are usually sharply circumscribed, surrounded by normal villi, and even in the most severe cases affect no more than 50% of total villi. Secondary changes in

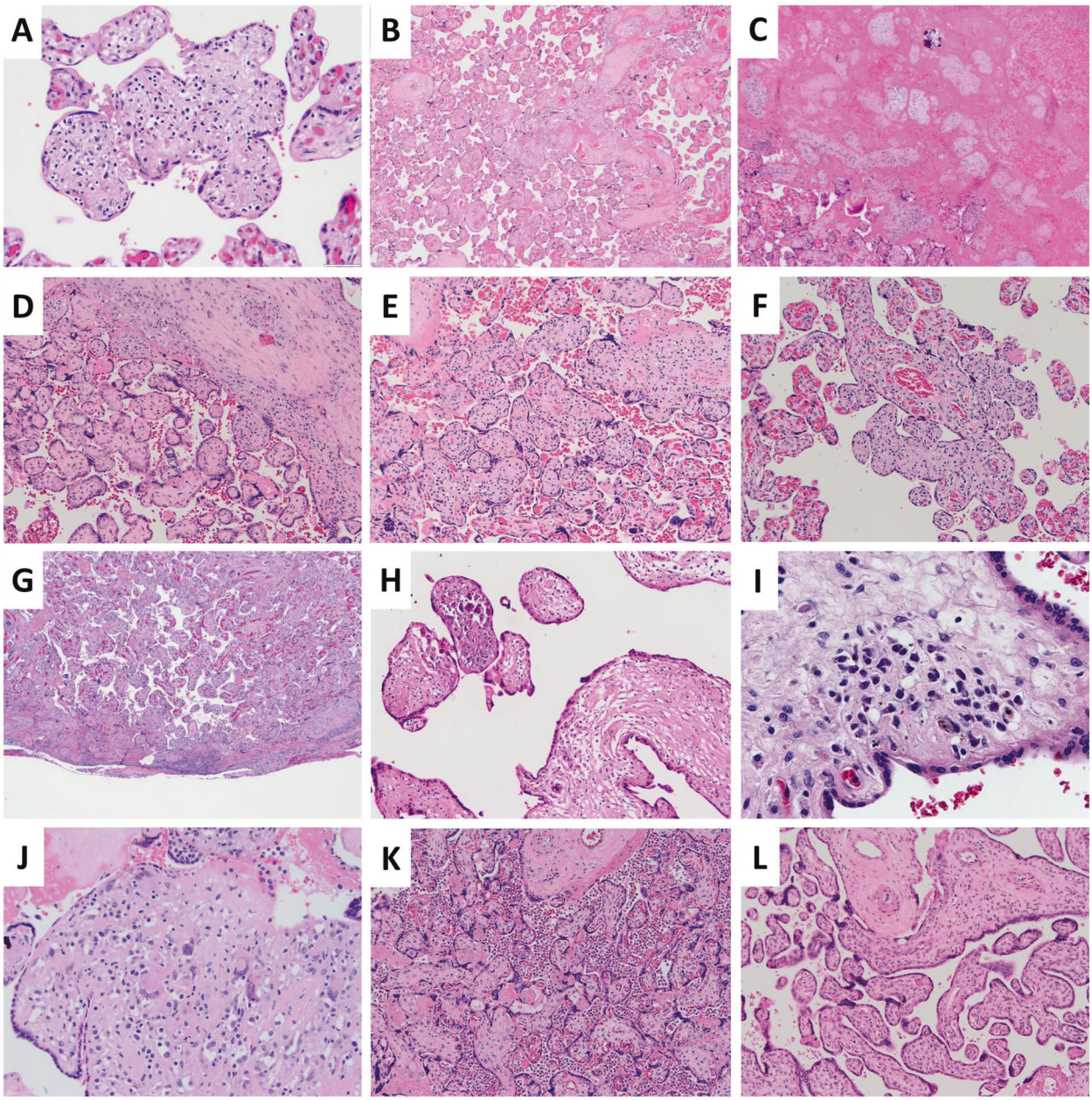

Fig. 4 Findings consistent with villitis of unknown etiology (VUE) and mimics. A Cluster of distal villi with VUE showing small lymphocytes, activated monocyte-macrophages, and focal degenerative changes in the villous stroma and overlying trophoblast in a background of normal villi (H&E 200×). **B** Foci of VUE can be detected at scanning magnification by the finding of small clusters of loosely agglutinated villi with decreased vascularity and an asymmetric small mononuclear cell infiltrate (H&E 40×). **C** Extensive VUE is commonly associated with accumulation of perivillous fibrin and secondary villous degenerative changes (H&E 40×). **D** VUE involving fetal stem villi can lead to obliteration of muscularized arteries (upper right) with adjacent downstream avascular terminal villi (H&E 100×). **E** High grade chronic villitis (VUE) is defined by chronic inflammation involving the stroma of 10 or more contiguous chorionic villi. (H&E 100×). **F** Low grade chronic villitis (VUE) is defined by smaller (<10) numbers of contiguous inflamed villi (H&E 100×). **G** Basal villitis, usually accompanied by lymphoplasmacytic deciduitis, is limited to villi near or embedded in the basal plate (H&E 20×). **H** Chronic infectious (TORCH-type) villitis often shows stromal fibrosis, vacuolated macrophages, edema, and mineralization, features not typically prominent in VUE (H&E 100×). **I** Cytomegalovirus (CMV) villitis: any chronic villitis with plasma cells in the villous stroma is CMV until proven otherwise. Stromal hemosiderin is another typical feature (H&E 400×). **J** Focally granulomatous villitis can accompany toxoplasmosis, but unlike plasma cells and CMV, the correct diagnosis in most placentas with this finding is VUE (H&E 200×). **K** Chronic histiocytic intervillositis is a relatively rare lesion characterized by an exclusively intervillous infiltrate of monomorphic monocyte-macrophages. (H&E 100×). **L** Increased villous Hofbauer cells (fetal macrophages) are distinguished from VUE by a diffuse symmetric increase in cellularity, lack of lymphocytes, and absence of tissue injury (H&E 100×).

proximity to affected villi include excessive amounts of perivillous fibrin (Fig. 4C) and large contiguous foci of avascular villi (Fig. 4D). Either finding should prompt careful examination of the villous stroma for the pathognomonic asymmetric round cell infiltrate. Finally, a number of lesions in locations distant from affected villi can redirect a search for an associated VUE. Chronic deciduitis, usually with plasma cells, is common in VUE and virtually always present in the basal variant (see below). Other less commonly occasionally associated lesions include the previously discussed chronic (lymphocytic) chorioamnionitis, chorionic histiocytic hyperplasia, and eosinophilic/T-cell fetal vasculitis (Fig. 3H–K).

Subclassification, grading, and staging

Grading of VUE is binary with high grade being defined as multiple foci of inflammation, at least one containing 10 or more contiguous affected villi. The high grade category is separated into subcategories; diffuse, when >30% of all villi are affected, and patchy for the remainder (Fig. 4F). Low grade cases are also split into two subcategories; focal, when all of the smaller foci are on one slide, and multifocal, when more than one slide is involved (Fig. 4E). While usually limited to distal villi, VUE can spread to stem villi with accompanying chronic perivasculitis, stem vessel obliteration, and extensive AV (a process previously known as "fetal obliterative vasculopathy") [6]. This pattern has been associated with adverse neurologic outcomes and IUFD and should be highlighted in the placental report. Exclusively basal villitis is another special category that may have a separate pathogenesis, as suggested by a small proportion of B cells in the inflammatory infiltrate (Fig. 4G) [91]. It is not usually associated with IUGR or IUFD, but rather is increased in cases of premature labor, MVM, and placenta accreta spectrum [8, 92]. The most salient features of VUE are summarized in Table 6.

Table 6 Villitis of unknown etiology (VUE): summary.

Defining feature	
	Small lymphocytes with stromal reaction in terminal villi
Extent	
	Low grade: Focal: less than 10 contiguous villi per focus, one slide only
	Multifocal: less than 10 contiguous villi per focus, multiple slides
	High grade: Patchy: multiple foci, at least one with >10 contiguous villi
	Diffuse: >10 villi per focus, >30% total villi affected
	Ungradable, possibly high grade: single focus of >10 villi
Variant	
	Basal villitis (only) with or without lymphoplasmacytic deciduitis
Special features	
	Extensive perivillous fibrin
	Stem vessel obliteration and associated large foci of avascular villi
Differential diagnosis/pitfalls	
	Chronic infectious villitis (TORCH infection)
	Chronic histiocytic intervillositis
	Increased villous Hofbauer cells

Differential diagnosis and pitfalls

The most important differential diagnosis for VUE is congenital infection of the TORCH-type [81]. The histologic pattern of TORCH infections is variable ranging from a diffuse histiocytic infiltrate with villous edema and rare lymphocytes to a diffuse sclerotic pattern with marked villous fibrosis and calcification (Fig. 4H), but only occasionally overlaps with the more sharply circumscribed foci seen in VUE. Villous plasma cells are not a feature of VUE. When identified, they are strongly suggestive of CMV even if inclusions are absent and immunohistochemical staining is negative (Fig. 4I) [93, 94]. CMV and other viral infections often target endothelial cells, so stromal hemosiderin is also more common in these cases. Granulomatous villitis is uncommon in VUE (Fig. 4J) and also a feature of placental toxoplasmosis [95]. This finding should prompt careful examination for pseudocysts in the umbilical cord stroma and, in selected cases, immunostaining. Nevertheless, it is important to emphasize that most cases with histiocytic giant cells are VUE, not toxoplasmosis. Chronic histiocytic intervillositis is a distinct idiopathic chronic inflammatory condition characterized by abundant immature CD68-positive monocytes in the intervillous space (Fig. 4K) [96]. This rare lesion is another important cause of recurrent pregnancy loss. Any evidence of inflammation in the villous stroma (VUE) disqualifies a case from this category. Both FVM with extensive avascular villi and diffuse perivillous fibrin deposition (maternal floor infarction) mimic some aspects of high grade VUE. However, again, any evidence of a villous lymphocytic infiltrate places the case in the VUE category.

A pitfall leading to overdiagnosis of VUE is increased villous Hofbauer cells (Fig. 4L). Hofbauer cells are fetally-derived stromal macrophages that may occasionally be increased in number or activation state with ACA, hydrops fetalis, MVM, delayed villous maturation, or chronic abruption [97]. The key to avoiding misdiagnosis is to appreciate the symmetrical distribution of these macrophages, the lack of small lymphocytes, and the absence of any associated stromal tissue reaction. Immunostaining for CD3 can be helpful to exclude VUE if ambiguity exists.

Reporting

Despite its usefulness as an acronym, we do not use the term VUE in our clinical reports. Rather, we give a line diagnosis of chronic villitis, low or high grade, focal, multifocal, patchy, or diffuse, followed by associated features such as stem vessel obliteration, perivillous fibrin or avascular villi. The special case of a single focus with >10 contiguous affected villi is described as "ungradable, possibly high grade (single focus of >10 villi)". By convention, a single focus of low grade villitis is not reported. Basal villitis, usually with lymphoplasmacytic deciduitis, is reported separately.

Final comments

In conclusion, this review has focused on the diagnosis of the four most common patterns of placental injury and their differential diagnosis. In addition to the two rare important entities discussed above under the differential diagnosis of MVM and VUE (massive perivillous fibrin deposition (maternal floor infarction) and chronic histiocytic intervillositis), some other important placental processes outside of the scope of this review include placental abruption, villous capillary proliferative lesions, placenta accreta spectrum, multiple gestation, and increased circulating fetal nucleated red blood cells [25, 98–104]. Another important consideration, not yet fully explored, is the significance of multiple concurrent placental lesions, which can synergistically lead to adverse outcomes, particularly when they are severe and show temporal variation. As we have stressed throughout this review, the Amsterdam classification represents a major step forward for enhancing clinical utility, establishing pathophysiologic mechanisms, and standardizing nomenclature in placental pathology. Nevertheless, reliability of diagnosis is an elusive target and no doubt additional education efforts and refinements to the classification system will be necessary to fully realize its goals.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All relevant ethical standards were followed.

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