Sampling and Definitions of Placental Lesions

Amsterdam Placental Workshop Group Consensus Statement

T. Yee Khong, MD; Eoghan E. Mooney, MB, FRCPath; Ilana Ariel, MD, PhD; Nathalie C. M. Balmus, MD; Theonia K. Boyd, MD; Marie-Anne Brundler, MD; Hayley Derricott, BSc; Margaret J. Evans, FRCPath (Paeds); Ona M. Faye-Petersen, MD; John E. Gillan, MD; Alex E. P. Heazell, MBChB, PhD; Debra S. Heller, MD; Suzanne M. Jacques, MD; Sarah Keating, MD; Peter Kelehan, MD; Ann Maes, MD; Eileen M. McKay, MD; Terry K. Morgan, MD, PhD; Peter G. J. Nikkels, MD, PhD; W. Tony Parks, MD; Raymond W. Redline, MD; Irene Scheimberg, MD; Mirthe H. Schoots, MD; Neil J. Sebire, MD; Albert Timmer, MD, PhD; Gitta Turowski, MD; J. Patrick van der Voorn, MD; Ineke van Lijnschoten, MD; Sanne J. Gordijn, MD, PhD

• ***Context.***—**The value of placental examination in investigations of adverse pregnancy outcomes may be compromised by sampling and definition differences between laboratories.**

Objective.—**To establish an agreed-upon protocol for sampling the placenta, and for diagnostic criteria for placental lesions. Recommendations would cover reporting placentas in tertiary centers as well as in community hospitals and district general hospitals, and are also relevant to the scientific research community.**

Data Sources.—**Areas of controversy or uncertainty were explored prior to a 1-day meeting where placental and perinatal pathologists, and maternal-fetal medicine specialists discussed available evidence and subsequently reached consensus where possible.**

Conclusions.—**The group agreed on sets of uniform sampling criteria, placental gross descriptors, pathologic terminologies, and diagnostic criteria. The terminology and microscopic descriptions for maternal vascular malperfusion, fetal vascular malperfusion, delayed villous maturation, patterns of ascending intrauterine infection, and villitis of unknown etiology were agreed upon. Topics requiring further discussion were highlighted. Ongoing developments in our understanding of the pathology of the placenta, scientific bases of the maternofetoplacental triad, and evolution of the clinical significance of defined lesions may necessitate further refinements of these consensus guidelines. The proposed structure will assist in international comparability of clinicopathologic and scientific studies and assist in refining the significance of lesions associated with adverse pregnancy and later health outcomes.**

(*Arch Pathol Lab Med.* 2016;140:698–713; doi: 10.5858/arpa.2015-0225-CC)

Accepted for publication October 2, 2015.

Published as an Early Online Release May 25, 2016.

From SA Pathology, Women's and Children's Hospital, University of Adelaide, North Adelaide, Australia (Dr Khong); the Department of Pathology, National Maternity Hospital, Dublin, Ireland (Drs Mooney and Kelehan); the Department of Pathology, Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel (Dr Ariel); the Department of Pathology, Kennemer Gasthuis, Haarlem, the Netherlands (Dr Balmus); the Department of Pathology, Boston Children's Hospital, and the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Dr Boyd); the Departments of Pathology and Laboratory Medicine, and Pediatrics, University of Calgary, Calgary, Alberta, Canada (Dr Brundler); the Maternal & Fetal Health Research Centre, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom (Ms Derricott); the Department of Pathology, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom (Dr Evans); the Department of Pathology, University of Alabama at Birmingham, (Dr Faye-Petersen); the Department of Pathology, Rotunda Hospital, Dublin, Ireland (Dr Gillan);the Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, and St Mary's Hospital, Manchester Academic Health Science Centre, Manchester, United Kingdom (Dr Heazell); the Department of Pathology and Laboratory Medicine, Rutgers-New Jersey Medical School, Newark (Dr Heller); Department of Pathology, Hutzel Women's Hospital/Harper University Hospital, Wayne State University School of Medicine, Detroit, Michigan (Dr Jacques); the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada (Dr Keating); the Department of Forensic Medicine, Netherlands Forensic Institute, The Hague, the Netherlands (Dr Maes); the Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia (Dr McKay); the Departments of Obstetrics and Gynecology, and Pathology, Oregon Health and Science University, Portland (Dr Morgan); the Department of Pathology, University Medical Center, Utrecht, the Netherlands (Dr Nikkels); the Departments of Pathology, and Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania (Dr Parks); the Department of Pathology, University Hospitals Case Medical Center and Case Western Reserve University School of Medicine, Cleveland, Ohio (Dr Redline); the Department of Pathology, Royal London Hospital, London, United Kingdom (Dr Scheimberg); the Departments of Pathology and Medical Biology (Drs Schoots and Timmer) and Obstetrics and Gynecology (Dr Gordijn), University Medical Center Groningen, University of Groningen, the Netherlands; the Department of Pathology, Great Ormond Street Hospital, London, United Kingdom (Dr Sebire); the Department of Pathology, Center for Perinatal and Pregnancy-Related Pathology, Oslo University Hospital, Oslo, Norway (Dr Turowski); the Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands (Dr van der Voorn); and the Department of Pathology, Laboratorium voor Pathologie en Medische Microbiologie, Eindhoven, the Netherlands (Dr van Lijnschoten). Drs Khong and Mooney contributed equally to this paper.

The authors have no relevant financial interest in the products or companies described in this article.

Reprints: T. Yee Khong, MD, Department of Histopathology, Women's and Children's Hospital, 72 King William Rd, North Adelaide, SA 5006, Australia (email: yee.khong@adelaide.edu.au).

Stillbirths and neonatal deaths are a global problem, with more than 6.4 million deaths occurring each year.[1,2] A systematic review concluded that pathology of the placenta, cord, or membranes is attributed as a cause or contributory to stillbirth in 11% to 65% of cases in various classifications, depending on the classification used.[3] This review also found that protocols of sampling the placenta varied among institutions and varying definitions of placental lesions made comparisons or efforts to direct improvement in perinatal care and outcomes difficult.[3]

Since the publication of a practice guideline for examining the placenta,[4] definitions have been further refined and new lesions have been described. Thus, a consensus-determined protocol for sampling the placenta and collectively agreed-upon definitions of placental lesions are cogently needed. The following describes the consensus from an international workshop convened to address these issues. Its authors propose that its placental gross descriptors, sampling specifications, pathologic terminologies, and diagnostic criteria represent a critically needed systematic approach, and one that is suitable for worldwide implementation. Moreover, we propose that the following protocols and definitions can be applied by general practice pathologists and improve the value of placental pathology and perinatal autopsy reports.

DESIGN

Practicing perinatal pathologists and placental pathologists were invited (by authors T.Y.K., E.E.M., and S.J.G.) to participate in a 1-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 people who were contacted directly; 40 people 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. The group also built on a well-constructed series of definitions of three placental patterns of disease (fetal vascular obstruction, maternal vascular underperfusion [then termed], and inflammatory conditions).[5–7] Twenty-six pathologists were able to attend and participate in the workshop held in Amsterdam, the Netherlands, in September 2014. Following discussion and presentation of evidence, where available, the group constructed recommendations to standardize definitions of lesions.

RECOMMENDATIONS

Sampling the Placenta

Participants agreed that standardizing gross examination and histologic sampling of the placenta is important because focal lesions should not be missed, and because the comparison between studies of frequencies and significance of lesions is dependent on sampling methods. It was acknowledged that a range of practitioners, other than pathologists with an interest in the placenta, perform gross evaluation and sampling of placentas, including nonspecialist pathologists, residents, and pathology assistants. In addition, pathology laboratories are located in tertiary hospitals as well as community or district general hospitals. Cost imperatives were also considered and weighed relative to the possible yield versus the number of blocks submitted.

Placental Weight.—Description of the placenta should include the placental weight trimmed of extraplacental membranes and umbilical cord, and notation of whether the placenta was fresh or fixed when measured. Any prior sampling of the placental parenchyma should also be documented. Any disruption of the basal plate should be noted.

The placental weight is a surrogate for placental function,[8] and fetoplacental weight ratio has been suggested as a possible indicator of adequacy of placental reserve capacity in fetal growth restriction (FGR).[9]

Where possible, contemporary placental weight standards derived from the respective local or similar population should be used.

Fixation of the placenta will affect its weight, with an increase of 3% to 6%,[10] and it was acknowledged that some lesions are more easily identified after fixation, whereas others are better identified in the fresh state. It was felt that recording the duration the placenta had been fixed prior to examination was not feasible because there may be a variable interval between delivery and specimen receipt in the laboratory.

Placental Disk Dimensions.—Description of the placenta should include the measurement of the placenta in three dimensions: the maximal linear dimension (length), the greatest dimension of the axis perpendicular to this linear measurement (width), and the mural minimal and maximal thickness.

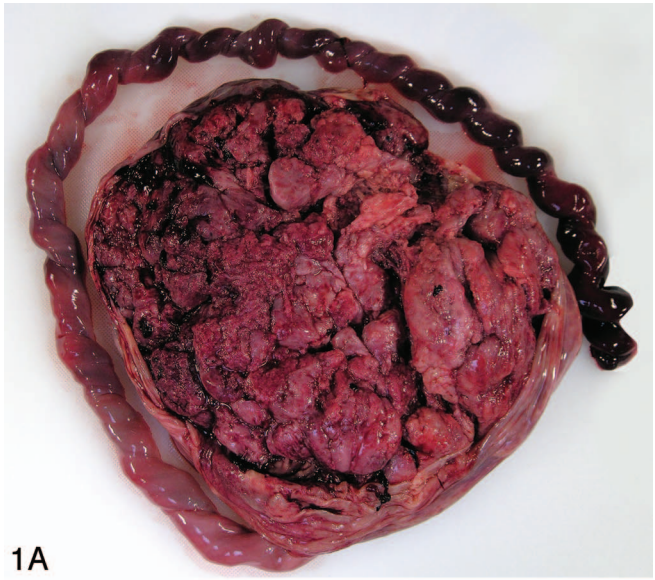
There is some evidence to suggest that shape and size of the placenta are factors that may be statistically associated with pregnancy complications (FGR, reduced fetal movements) and an individual's long-term health.[11–18]

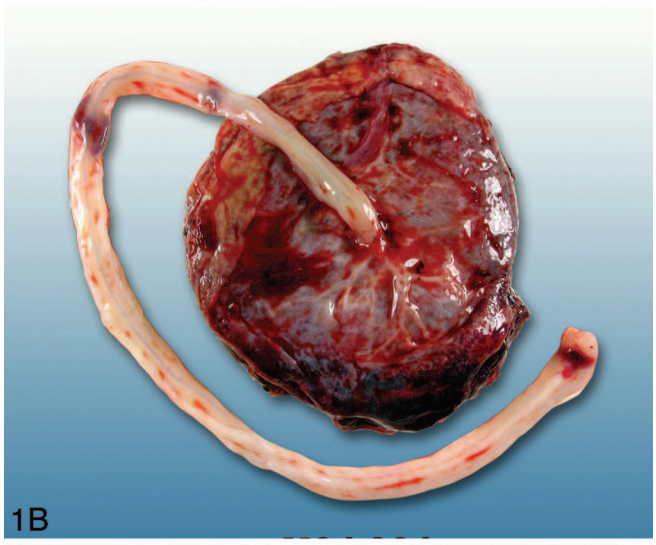
Measuring the placental dimensions will also allow further refinement of determining the functional reserve of the placenta by correlation of size of any lesions with the overall dimensions of the placenta.

Description of Umbilical Cord.—Description of the umbilical cord should include the average diameter of the cord; length; site of insertion in relation to the center/margin of the placenta, determined by measuring the distance between the insertion site and the nearest placental margin; the presence of strictures; and whether the cord appears to be hypocoiled or hypercoiled (Figures 1 and 2). Segmental or localized areas of hypercoiling should be recorded. Direction of coiling (handedness) should be noted if possible.

Thin umbilical cords are associated with FGR, whereas thick cords are associated with maternal diabetes and with fetal hydrops.[19–21] Excessively long and short cords can be associated with adverse outcomes.[22–26]

Marginal (<1 cm from the nearest margin)[27] and velamentous insertions, but not peripheral (<3 cm from the nearest margin)[28] insertions, are associated with an increased risk of adverse pregnancy outcomes, including preterm delivery.[28] Hypocoiling (<1 coil per 10 cm) and hypercoiling (>3 coils per 10 cm) may be associated with adverse outcomes in some cases.[29–32] Opinion was divided about the best way to assess coiling, especially because cords are often incompletely submitted.[33] Fixation of the





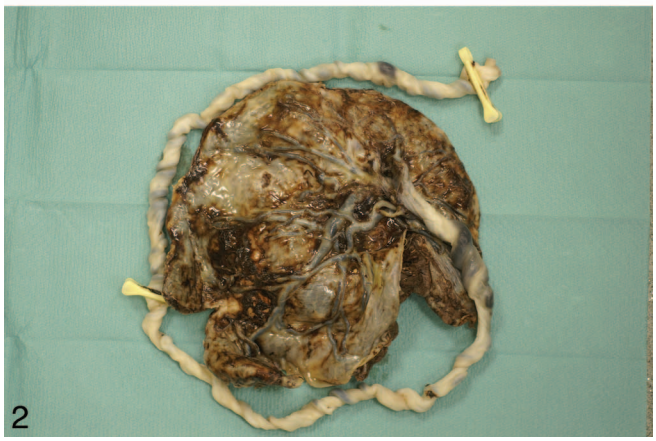


Figure 1. *A, A hypercoiled umbilical cord. B, A hypocoiled cord.*

Figure 2. *A long and hypercoiled umbilical cord with areas of relatively less coiling (eg, lower right).*

cord will affect the length[34] and therefore the coiling index, underscoring the importance of stating whether the placenta was fresh or fixed when pathologic examination was performed.

Because not all of the cord may be received and because the significance of a localized site or segmental sites of hypercoiling (Figure 2) is unclear,[33] it was felt that such a nonuniform finding should be recorded until there was clarity regarding its significance. However, deep grooves between coils in hypercoiled cords have been associated with stillbirth[35] and should be reported.

Left twist, defined as diagonal seams running from upper left to lower right, is most common. The clinical significance of left versus right twist remains unclear, but it may useful to document this on a research basis.

Description of Membranes.—Description of the membranes should include the color/opacity and completeness. Recording the shortest distance between the site of rupture to the placental edge may be useful in some cases of placenta previa if the rupture was at the edge, but the group was divided on this recommendation. If circumvallate or circummarginate, the percentage of the circumference involved should be noted.

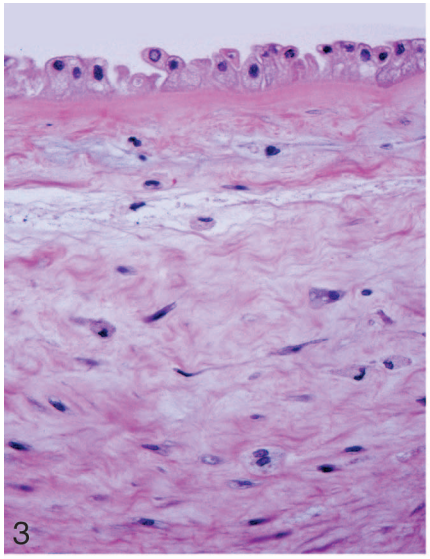
Circumvallation may be associated with bleeding in early pregnancy and may show iron deposition in the membranes, sometimes with a yellow-brown or brown discoloration.[36] Iron and meconium pigments are detectable on histology, and notation of abnormal appearance of the membranes grossly acts as a reminder to the pathologist at microscopic examination (Figure 3).

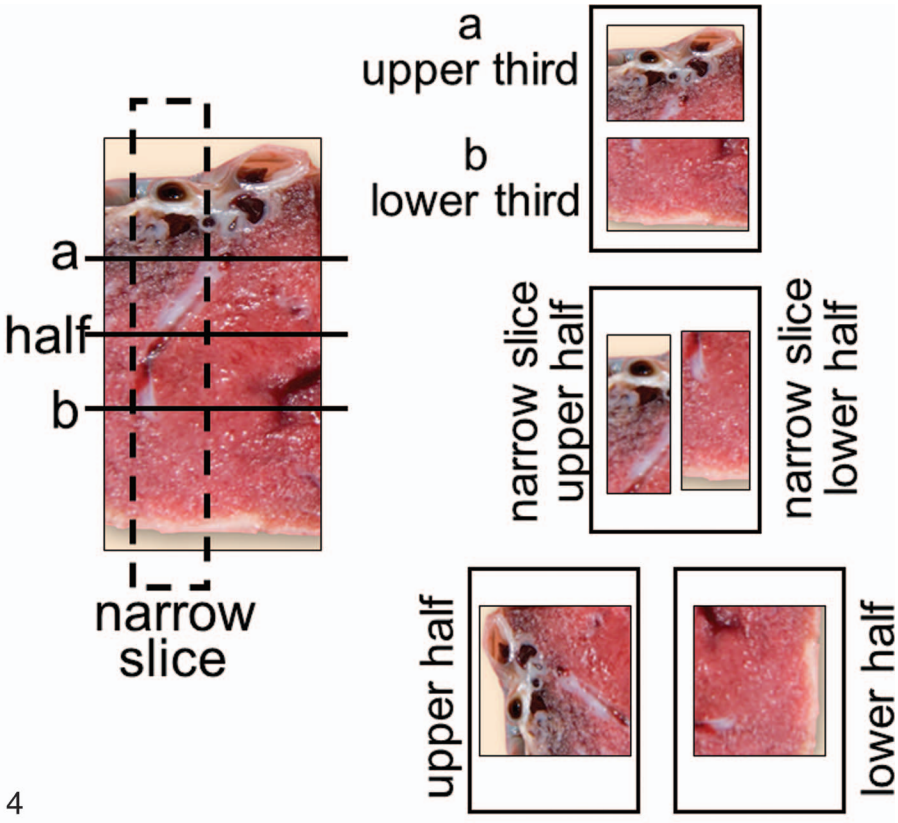
Sampling of Cord, Membranes, and Placental Disk.—Submit 4 blocks as a minimum: 1 block to include a roll of the extraplacental membranes from the rupture edge to the placental margin, including part of the marginal parenchyma; and 2 cross sections of the umbilical cord, one from the fetal end and another approximately 5 cm from the placental insertion end. Three other blocks each containing a full-thickness section of normal-appearing placenta parenchyma should be submitted. Full-thickness samples should be taken from within the central two-thirds of the disc and include one adjacent to the insertion site itself. If the transmural thickness is greater than the length of the cassette, two options are available: the upper third (chorionic plate and subjacent tissue) and lower third (basal aspect) of the parenchyma can be submitted in one cassette, or the gross slice can be divided into two and submitted in two cassettes (ie, a fifth block may be required; Figure 4).

A full-thickness sample should be taken from close to the umbilical cord insertion site to document fetal vascular ectasia and fetal and/or maternal inflammatory response.

A consensus number of 3 parenchymal blocks was selected based on discussion on sampling of placental lesions (*vide infra*) and evidence to indicate that 62% of villitis, as a prime example of a (multi)focal lesion, would be identified.[37]

Description of Lesions.—Grossly identified lesions should be described with either an estimate of the percentage of the total parenchymal volume they affect or a measurement of the two maximal dimensions of each lesion. The number of lesions of the same gross appearance should be counted and stated as being single or multiple. The location(s) of the lesions should be stated: central/paracentral or peripheral. Lesions that are microscopically different may appear similar grossly. A block of the lesion (one of each type of lesion) should be sampled, with adjacent normal parenchyma if possible, in up to 3 additional blocks.





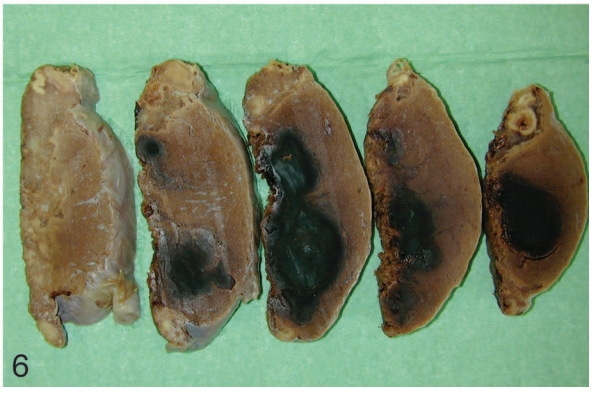


Figure 3. *A meconium-laden macrophage is seen in the amnion, whereas there is columnar metaplasia of the amniotic epithelium (hematoxylin-eosin, original magnification ×40).*

Figure 4. *Options for embedding a thick placental slide: preferred options are embedding the lower and upper thirds in 1 cassette or embedding the lower and upper halves in 2 separate cassettes.*

Figure 5. *Chronologic dating of infarcts is easier in the fixed placenta because the lesions are better demarcated: the older infarcts appear tan colored, whereas the fresher ones appear red and congested.*

Figure 6. *Fresh placental abruption resulting in marked congestion of the overlying placental parenchyma.*

The percentage of the total parenchymal volume provides an indication of the severity and likely effect of the lesion (see "Placental Weight").

In sampling the lesion, part of the lesion and of the adjacent normal area should be submitted for histology to enable placental reactions to the lesion to be elucidated.

Maternal Vascular Malperfusion of the Placental Bed

It is recommended that the term *maternal vascular malperfusion* (MVM) be used instead of *maternal vascular underperfusion* or other synonyms. Although much of the effects of inadequate spiral artery remodeling or spiral artery pathology manifest as a spectrum that includes FGR and preeclampsia,[38] high-velocity malperfusion may be detrimental to placentation in early pregnancy and placental function in later pregnancy.[39–41] There was considerable discussion on the relative merits of terms used to describe the features seen in cases of MVM, with the terms used below selected by consensus.

Placental features considered to be indicative of MVM include both gross and microscopic findings. Gross findings include placental hypoplasia, infarction, and

retroplacental hemorrhage (*vide infra*). Placental hypoplasia is reflected by a placental weight that is low for the stated gestational age and context (weight <10th centile) and/or a thin cord (<10th centile or <8-mm diameter at term). Any infarction seen in a preterm placenta and, at term, anything more than 5% of nonperipheral infarction must be described. Although marginal infarcts in a term placenta *may* have less meaning than in a preterm placenta, they should still be described.

Microscopic findings include abnormalities of villous development, which can be separated into distal villous hypoplasia, and accelerated villous maturation (*vide infra*). It should be recognized that many of these histologic findings will coexist in some placentas.

Terminology.—The term *maternal vascular malperfusion* should be used instead of the term *maternal vascular underperfusion*.

Infarcts.—In addition to the documenting of gross lesions, in the instance when potential infarcts are identified and one is a central lesion, the central lesion should be preferentially sampled for histology over a peripheral lesion. The suspected infarcts should also be qualified, where possible, as to whether they are recent or remote. When central hemorrhage is identified within a lesion, it should also be qualified and a sample taken for histology. When histology confirms that the hemorrhage is encased by infarction, the proposed term *infarction hematoma* should be used.[42]

Infarcts can be suspected by their generally pyramidal shape and usual involvement of the basal parenchyma or maternal floor of the placenta. Gross chronologic dating of infarcts is easier in the fixed placenta because the lesions are better demarcated (Figure 5).

Retroplacental Hemorrhage.—In addition to the recommendation of the documenting of gross lesions, in instances when a retroplacental hemorrhage is associated with indentation of the placental parenchyma, the indentation should be described, and two dimensions (length and width) or the percentage of maternal surface area involved should be recorded. Any clot that is separate from the placenta but submitted in the specimen container should be weighed and, if possible, measured in three dimensions. At least one sample of the area of retroplacental hemorrhage should be submitted for histology, which should include part of the basal plate.

Placental abruption is a clinical diagnosis and the correct descriptor for the pathologic finding is retroplacental hemorrhage or retroplacental hematoma.

The criteria for retroplacental hemorrhage have been published previously.[6] Grossly, there is blood accumulation on the maternal surface, with congestion and/or hemorrhage within or compression of the overlying parenchyma (Figure 6). Microscopically, there is blood accumulation beneath and dissecting the decidua and compression of the overlying intervillous space, with villous crowding, congestion, and/or intravillous hemorrhage with touching villi; there is also a smudged appearance, as evidence of early coagulation necrosis of the syncytiotrophoblast nuclei, and pale appearance of syncytiotrophoblast nuclei (Figures 7 through 9).

Chronicity of Infarction.—Early infarction and microscopic infarction can be diagnosed histologically, and these should be recorded in the body of the report.

Early infarcts are seen as crowding and congestion of villi, which may be hemorrhagic, accompanied by early loss of nuclear staining of the stroma. There may also be migration of neutrophils into the intervillous space, which may be compressed or obliterated (Figure 10). Later changes include necrotic changes (pyknosis and karyorrhexis of trophoblast), loss of trophoblast nuclear staining, and eventually ghost villi.

Distal Villous Hypoplasia.—Distal villous hypoplasia (DVH) is defined as the paucity of villi in relation to the surrounding stem villi. The villi are thin and relatively elongated-appearing, and syncytial knots are increased. Distal villous hypoplasia is more commonly seen with MVM in early pregnancy (<32 weeks of gestation).

This is best observed at low-power microscopy and by comparing the lower two-thirds of the thickness of the parenchyma to the subchorionic third (Figure 11). The diagnosis should be made when the features are seen in the lower two-thirds and involve at least 30% of 1 full-thickness parenchymal slide. It may be further graded as focal—finding of lesion in 1 full-thickness slide only—or diffuse—present in 2 or more full-thickness slides sampled. Diffuse distal villous hypoplasia is associated with early-onset FGR.[43]

Accelerated Villous Maturation.—Accelerated villous maturation is defined as the presence of small or short hypermature villi for gestational period, usually accompanied by an increase in syncytial knots.

By virtue of the use of this phrase, accelerated villous maturation may be difficult to recognize in a term placenta, but it is a reproducible pattern to diagnose prior to term. It is diagnosed by identifying a diffuse pattern of term-appearing villi with increased syncytial knots and intervillous fibrin, usually alternating with areas of villous paucity (Figure 12).

Syncytial knot prevalence has been studied at term,[44] and knots on more than 33% of villi may be regarded as increased.

Areas adjacent to infarcts should not be relied on for the diagnosis of accelerated villous maturation.

Accelerated villous maturation is a common pattern that may be found in mild, moderate, or severe forms of placental insufficiency, which includes FGR, preeclampsia, and preterm labor.[45]

Decidual Arteriopathy.—Decidual arteriopathy should be noted. The location should be stated as whether it is in the membrane roll or basal plate or both.

The elements include acute atherosis (Figure 13), fibrinoid necrosis with or without foam cells (Figure 14), mural hypertrophy (Figure 15), chronic perivasculitis (Figure 15, A), absence of spiral artery remodeling (Figure 16), arterial thrombosis (Figure 17), and persistence of intramural endovascular trophoblast in the third trimester (Figure 18).

Other Findings.—The consensus was that there is insufficient evidence at this stage that increased islands of fibrinoid with extravillous trophoblast (so-called X cells), placental pseudocyst (Figure 19), chorion laeve pseudocyst (Figure 20), and membranous decidual necrosis[46–48] are conclusively indicative of MVM.[49] Their documentation may facilitate further clinicopathologic studies.

Fetal Vascular Malperfusion

It is recommended that the term *fetal vascular malperfusion* (FVM) be used instead of *fetal thrombotic vasculopathy*. For severe forms of FVM, the term *high-grade FVM* will be used (see later). The lesions described under this umbrella of FVM are likely to be due to obstruction in fetal blood flow that could result from a number of conditions (eg, umbilical

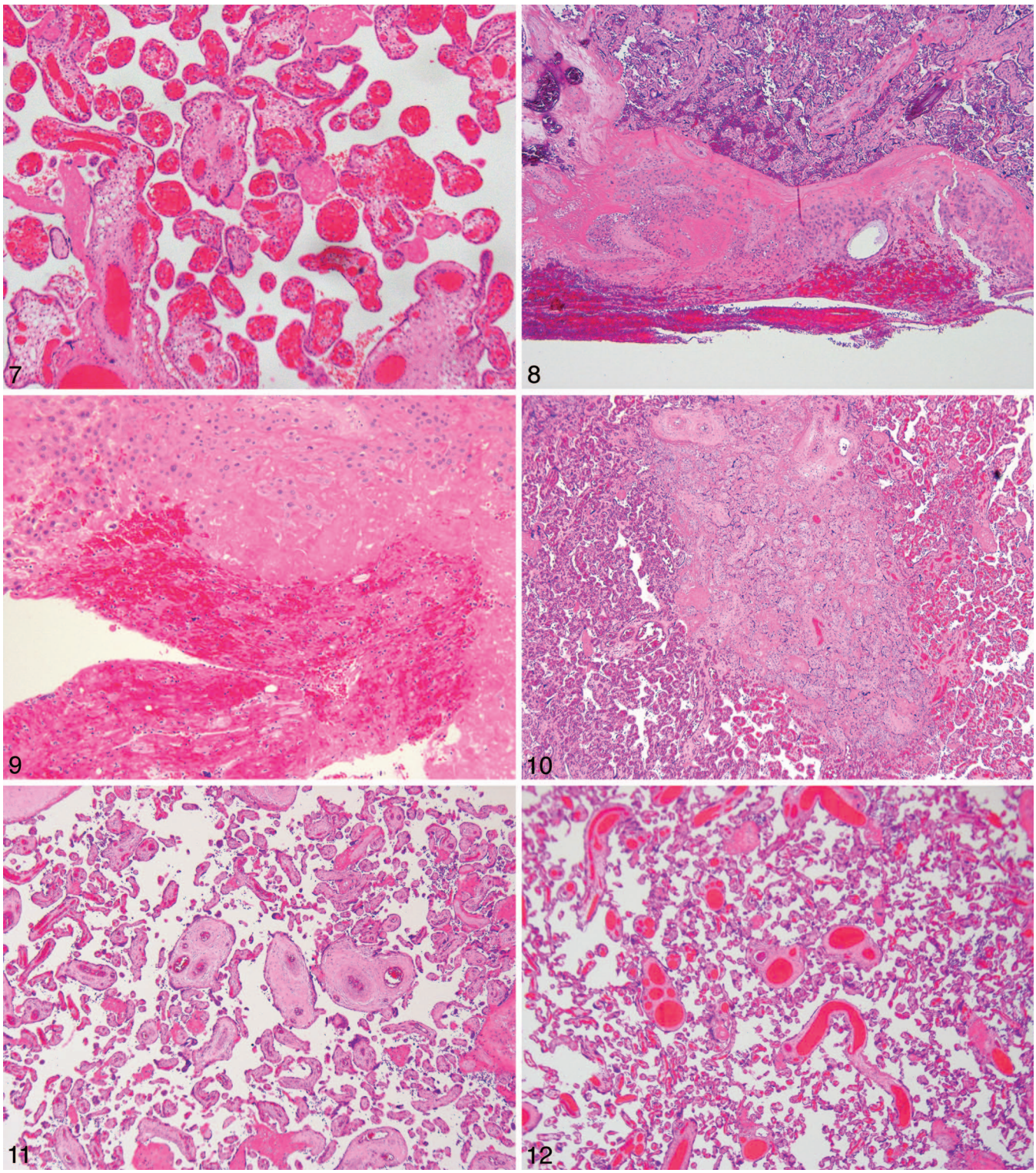


Figure 7. *Intravillous hemorrhage accompanying retroplacental hemorrhage (hematoxylin-eosin, original magnification ×10).*

Figure 8. *Dissection of the basal plate in retroplacental hemorrhage. There is congestion of the intervillous space immediately above the hemorrhage (hematoxylin-eosin, original magnification ×2).*

Figure 9. *Neutrophils as a vital reaction to the retroplacental hemorrhage (hematoxylin-eosin, original magnification ×40).*

Figure 10. *Early infarction showing crowding and compression of the intervillous space in the center of the infarct and congestion of villi around its periphery (hematoxylin-eosin, original magnification ×2).*

Figure 11. *Distal villous hypoplasia: there is a paucity of villi, many of which are thin and elongated (hematoxylin-eosin, original magnification ×4).*

Figure 12. *Accelerated villous maturation: there is a combination of areas with increased syncytial knots and intervillous fibrin deposition (hematoxylin-eosin, original magnification ×4).*

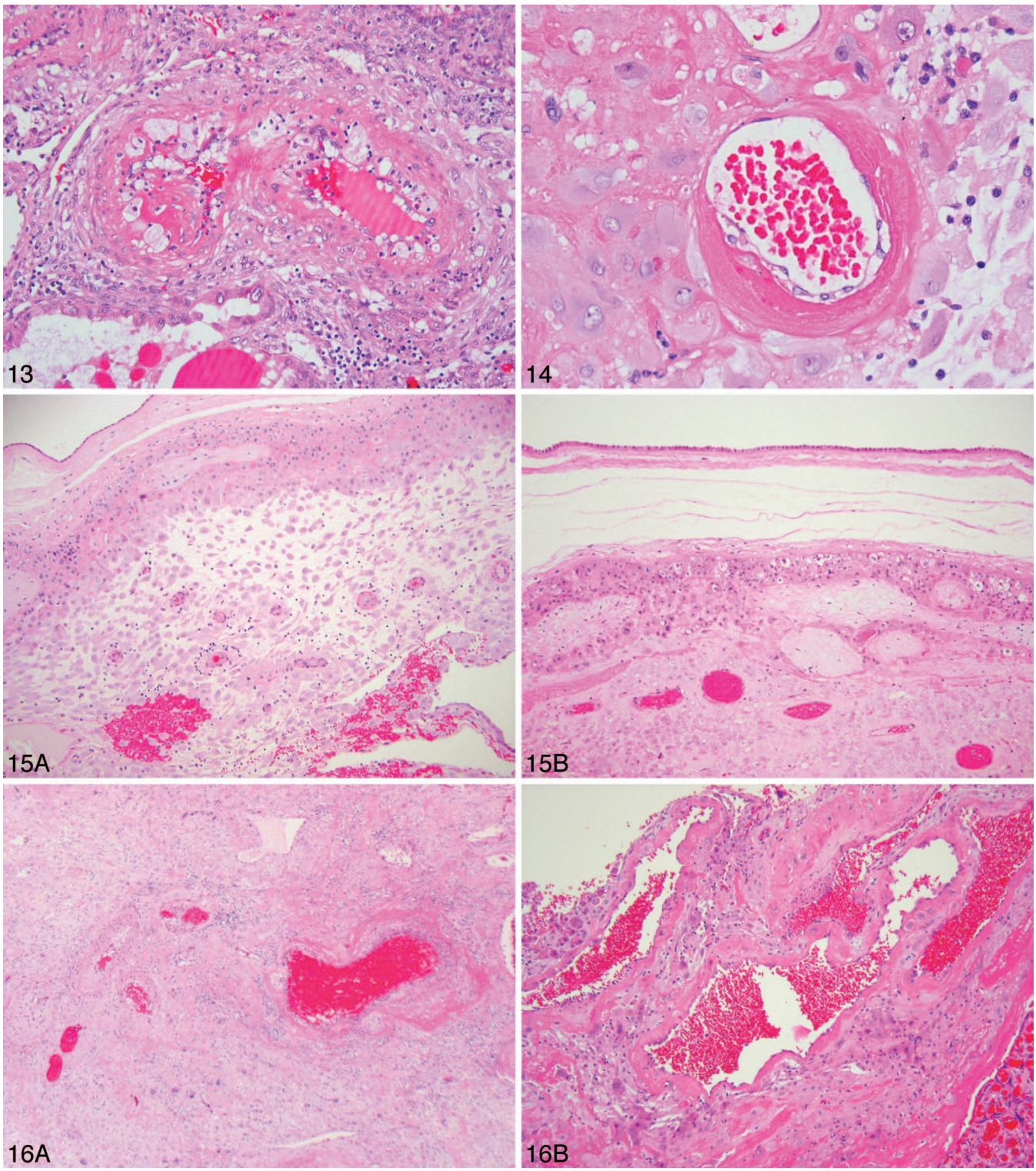
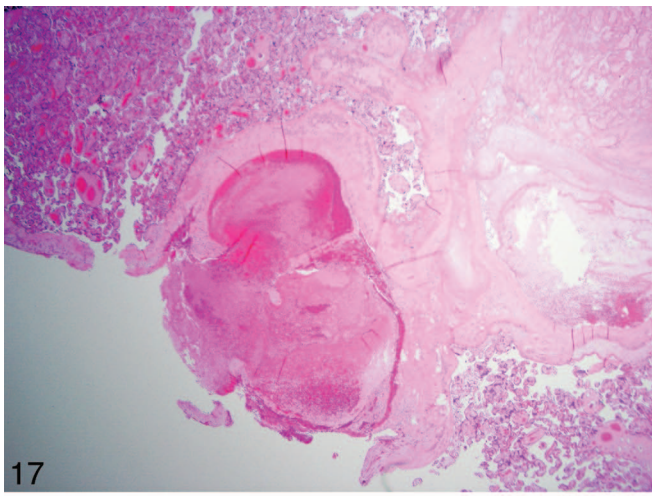


Figure 13. *Acute atherosis: there is fibrinoid necrosis with lipid-laden macrophages and a slight perivascular lymphocytic infiltrate (hematoxylin-eosin, original magnification ×20).*

Figure 14. *Fibrinoid necrosis of small maternal artery without an accompanying lipophage or lymphocytic component (hematoxylin-eosin, original magnification ×40).*

Figure 15. *A, Mural hypertrophy of maternal arteries in the decidua parietalis; note the scanty chronic perivascular lymphocytic infiltrate. B, Normal thin-walled maternal arteries in the decidua parietalis (hematoxylin-eosin, original magnification ×10).*

Figure 16. *A, Absence of spiral artery modeling with retention of musculoelastic elements in the arterial wall; note the acute atherosis affecting the vessel on the right. B, A remodeled spiral artery shows, by contrast, a distended caliber with replacement of the musculoelastic arterial wall by fibrinoid (hematoxylin-eosin, original magnification ×10).*



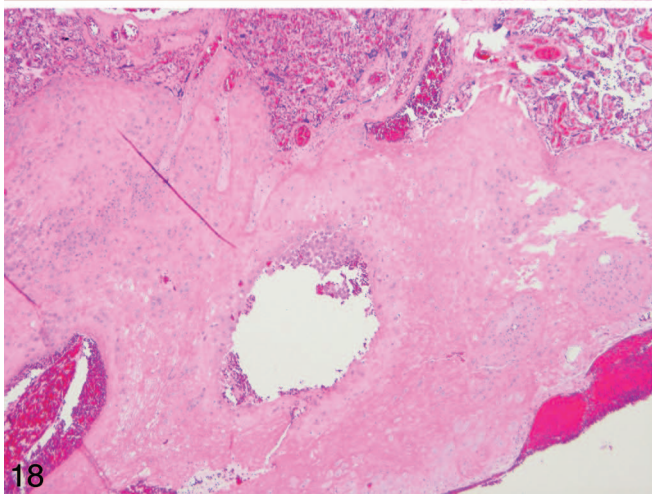


Figure 17. *Thrombosis of a maternal spiral artery with overlying infarction of the placenta (hematoxylin-eosin, original magnification ×2).*

Figure 18. *Persistence of endovascular trophoblast intraluminally (hematoxylin-eosin, original magnification ×2).*

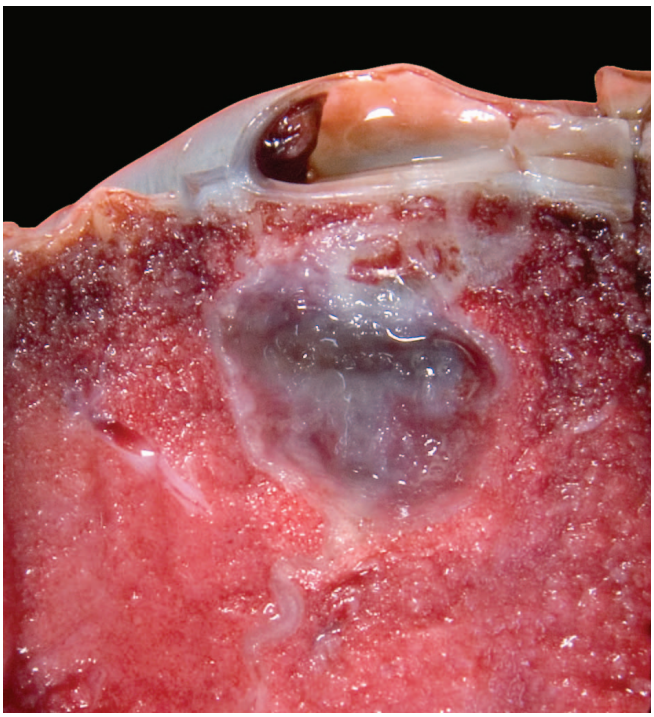


Figure 19. *Gross picture of a placental pseudocyst arising within a septum that is visible to the naked eye.*

cord lesions, hypercoagulability, complications of fetal cardiac dysfunction, such as hypoxia, etc.).[5,50–53]

At this stage of our understanding of the pathophysiology of fetal blood flow, findings consistent with FVM are thrombosis, segmental avascular villi, and villous stromal-vascular karyorrhexis. Other possible markers, such as vascular intramural fibrin deposition, stem vessel obliteration/fibromuscular sclerosis, and vascular ectasia, should also be sought.

All of the features of FVM have been described in placentas from live-born individuals and in stillbirths, and it can be difficult to tell with confidence whether the findings of FVM in an intrauterine death are due to a cause, such as thrombophilia or an obstruction, or be attributable to involutional or degenerative changes following fetal demise.[54] Thrombosis would be considered to be a premortem process. Finding of a discreet population of avascular villi may be possible in some cases of intrauterine death, where they contrast with the more cellular pattern of villous involution.

Two patterns of FVM are recognized, and either may be low grade or high grade. The first is segmental FVM, indicating thrombotic occlusion of chorionic or stem villous vessels, or stem vessel obliteration—although the distribution of the lesions is segmental, the thrombus or obstruction would be expected to result in complete obstruction to the villi downstream. The second is global FVM, indicating partially obstructed umbilical blood flow with venous ectasia, intramural fibrin deposition in large vessels, and/or small foci (<5 villi per focus) of avascular or karyorrhectic villi—the obstruction is partial or intermittent, but the lesions can be distributed over much of the placenta. The term *segmental* was chosen to reflect nomenclature used in other organ systems.

Terminology.—The term *fetal vascular malperfusion* should be used. The term *high-grade fetal vascular malperfusion* should be reserved for a severe form of FVM.

High-grade FVM is manifest by the finding of more than one focus of avascular villi (a cumulative assessment of ≥45 avascular villi over 3 sections examined or an average of >15 villi per section) with or without thrombus, *or* 2 or more occlusive or nonocclusive thrombi in chorionic plate or major stem villi, *or* multiple nonocclusive thrombi.

Thrombosis.—Whether the thrombosis is arterial or venous should be specified when possible. The location(s) of the thrombosis should be specified as to whether it is at the umbilical, chorionic plate, or stem vessel vascular level, or any combination thereof.

It may be unclear whether the fetal venous or arterial circulations are affected. However, in the chorionic plate arteries overlie corresponding veins and thrombosed vessels are thus potentially grossly distinguishable from one another (Figure 21). Specification of the location(s) of the thrombosis may clarify whether thrombosis located anywhere in the fetal vascular tree has the same clinical connotations.

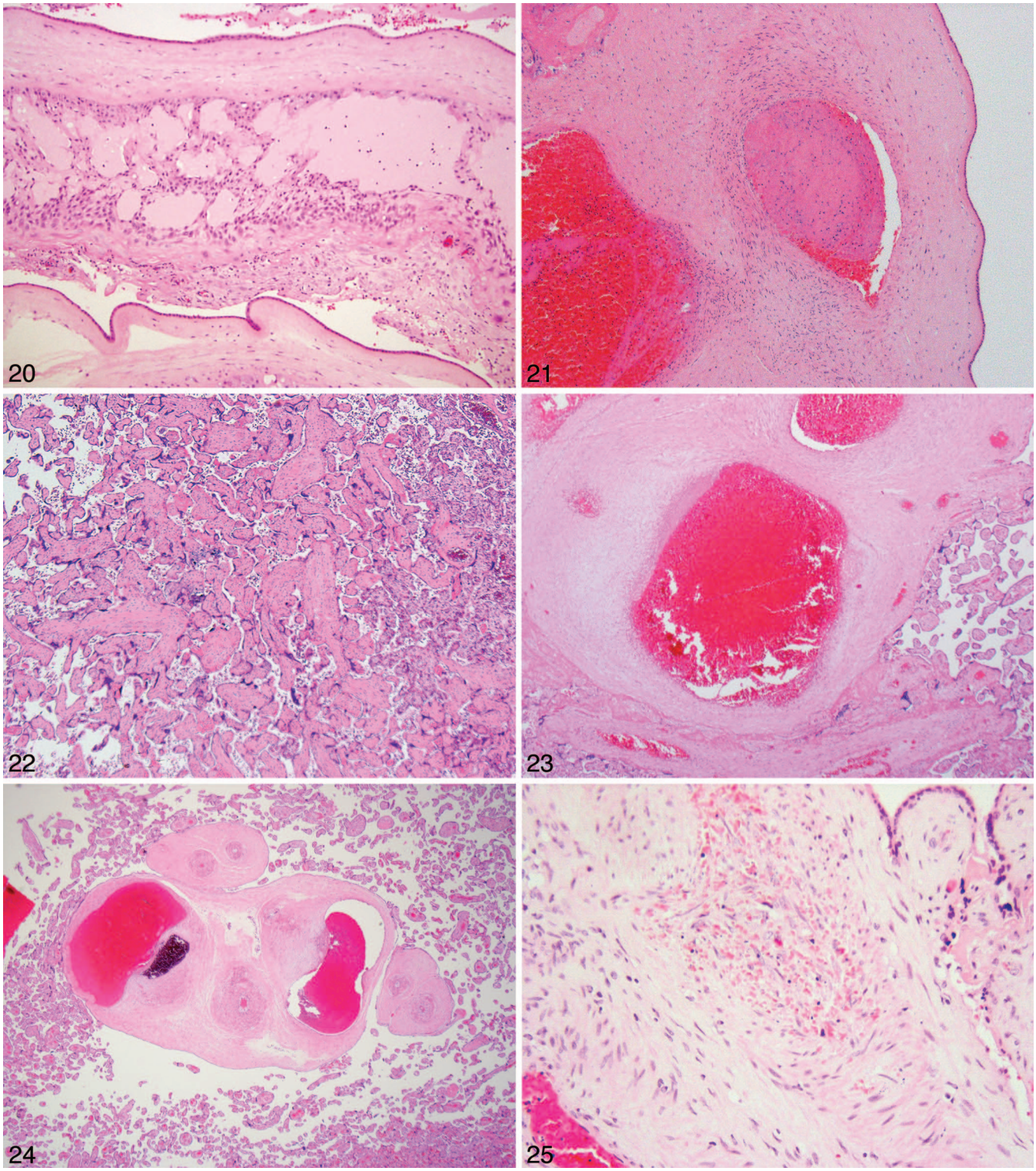


Figure 20. *Contiguous pseudocysts in the chorion laeve (hematoxylin-eosin, original magnification ×10).*

Figure 21. *Thrombosis of a fetal artery (overlying a vein) in the chorionic plate (hematoxylin-eosin, original magnification ×10).*

Figure 22. *A large focus of avascular villi, to the right of which vascularized villi are seen (hematoxylin-eosin, original magnification ×4).*

Figure 23. *Intramural fibrin deposition in a large main stem vessel (hematoxylin-eosin, original magnification ×4).*

Figure 24. *Intramural fibrin deposition and calcification, indicating remoteness of lesion, within a wall of the large fetal vessel (hematoxylin-eosin, original magnification ×2).*

Figure 25. *Villous stromal-vascular karyorrhexis: karyorrhexis of fetal cells with preservation of surrounding trophoblast (hematoxylin-eosin, original magnification ×40).*

Avascular Villi.—Avascular villi should be qualified in distribution and extent.

The criteria for avascular villi that have been published previously[5] are amended slightly. Small foci are the finding of 3 or more foci of 2 to 4 terminal villi showing total loss of villous capillaries and bland hyaline fibrosis of the villous stroma. Intermediate foci are 5 to 10 villi, and large foci are more than 10 villi (Figure 22).

Intramural Fibrin Deposition.—*Intramural fibrin deposition* is the preferred term to replace *intimal fibrin cushion*. It should be qualified as being isolated if there is no more than one such lesion per slide. Whether the lesion is recent or remote should be noted.

The location of the fibrin deposition is subendothelial or intramuscular, and thus intramural. It is also noted that the depositions are, by definition, nonocclusive. The criteria for intramural fibrin deposition have been published previously[5]: fibrin or fibrinoid deposition (subendothelial or intramuscular) within the wall of large fetal vessels (indicates recent; Figure 23), with calcification (indicates remote; Figure 24).

Although intramural fibrin deposits likely reflect global FVM, the significance of finding an isolated intramural fibrin deposition is unclear. As such, quantification may facilitate further clinicopathologic studies.

Villous Stromal-Vascular Karyorrhexis.—*Villous stromal-vascular karyorrhexis* is the term preferred to *hemorrhagic endovasculitis*.

Alternative terms were considered for this lesion, but it was felt that the descriptive term matched the finding of the lesion. *Hemorrhagic endovasculitis* was not preferred because it connotes an inflammatory cause and is not clinically useful. The criteria for villous stromal-vascular karyorrhexis that have been published previously[5] are amended slightly: 3 or more foci of 2 to 4 terminal villi showing karyorrhexis of fetal cells (nucleated erythrocytes, leukocytes, endothelial cells, and/or stromal cells) with preservation of surrounding trophoblast (Figure 25).

Stem Vessel Obliteration.—*Stem vessel obliteration* (synonymous with fibromuscular sclerosis) should be used instead of the term *stem vessel endovasculopathy*.

In stem vessel obliteration there is marked thickening of the vessel wall and resultant obliteration of the vascular lumen (Figure 26).

Vascular Ectasia.—Vascular ectasia, when it is observed histologically, should be noted.

The cause of vascular ectasia is not clear at this stage and may be nonspecific or related to umbilical cord compromise in combination with FVM. Vascular ectasia is characterized by the finding of vessels that are four times the luminal diameter of the surrounding corresponding vessel (Figure 27).[55]

Delayed Villous Maturation

It is recommended that the term *delayed villous maturation* be used instead of *villous maturation defect*, *variable villous maturation*, or *villous dysmaturity*. This lesion is seen usually after 36 weeks and rarely before 34 weeks of gestation and is characterized by a monotonous villous population with reduced numbers of vasculosyncytial membranes for the period of gestation, as well as a continuous cytotrophoblast layer and centrally placed capillaries.[56–59]

This term was preferred because villi throughout the cotyledon differ physiologically, and the term *dysmaturity*, which connotes different aspects of maturation, was felt to be too nonspecific, whereas the term *variable villous maturation* may be taken to reflect the physiologic villous pattern. *Villous maturation defect* was also considered to be nonspecific and could equally mean accelerated as well as delayed maturation. More cogently, it was felt that it was easier to conceptualize delayed villous maturation as being the opposite of accelerated villous maturation.

Terminology.—The use of the term *delayed villous maturation* is recommended.

The lesion is defined by a monotonous villous population (defined as at least 10 such villi) with centrally placed capillaries and decreased vasculosyncytial membranes, recapitulating the histology in early pregnancy (Figure 28). The diagnosis should be made when it is present in at least 30% of 1 full-thickness parenchymal slide.

Proposed Grading Schema.—Grading of the lesion is suggested at this juncture according to a proposed schema: focal, which is a finding of the lesion in 1 full-thickness parenchymal slide only, and diffuse, which is a presence in 2 or more full-thickness slides sampled.

The thresholds for significance of this lesion are unclear at present, and grading the lesion may help determine the appropriate levels.

Ascending Intrauterine Infection.—The participants recognized that ascending intrauterine infection is clinically important and that its histologic documentation forms a substantial amount of the clinically indicated placental pathology workload. There was agreement to emphasize that histologic chorioamnionitis may not be equivalent to clinical chorioamnionitis. There was, however, debate around whether to describe the stage and grade of inflammation in the reports.

Location and Characteristics of Inflammation.—The topography and constituents of the inflammatory response should be documented.

The group felt that for the general pathologist, not missing the inflammation was more important than the grading and staging of the inflammation (*vide infra*). Describing the topography of the inflammation will allow separation of the maternal from the fetal inflammatory response. This is thought to be important because there is evidence that poor fetal outcomes are more often associated with a fetal inflammatory response.[60–63] Chronicity of inflammation may have clinical implications different from those of a purely acute response, and should therefore be documented.

Subchorial Inflammation.—The presence of neutrophils in the subchorial intervillous space or beneath the chorion laeve layer in the absence of inflammation elsewhere, is not synonymous with acute chorioamnionitis and should be reported as subchorionitis (Figure 29).

Patchy accumulation of more than occasional polymorphonuclear leukocytes in the subchorionic fibrin and/or at the choriodecidual interface in the decidua represents an early stage of the response to amniotic fluid infection, whereas chorioamnionitis means exactly what it says, that is to say, inflammation in the chorion and amnion (Figure 30).

Grading and Staging.—Grading and staging of the inflammation are encouraged. The structure proposed by the Society for Pediatric Pathology[7] provides a template and definitions for both (Table).

Involvement of Artery or Vein or Both.—Which fetal vessels show an inflammatory response should be specified.

Evidence suggests a difference in cytokine levels between umbilical arteritis and umbilical phlebitis,[64] and a correlation between cytokine levels and the number of vessels involved.[64,65] Higher rates of adverse neonatal outcomes

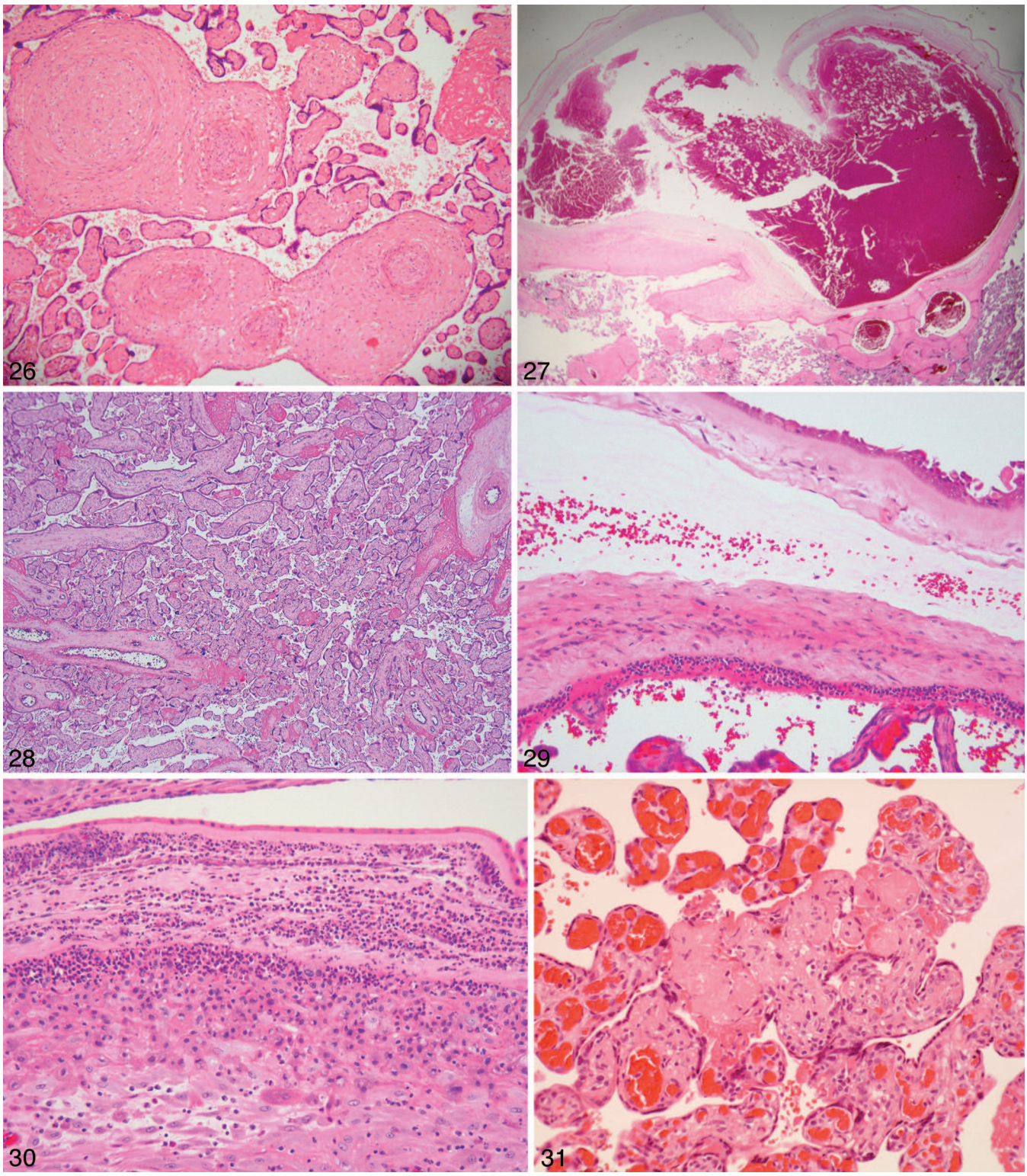


Figure 26. *Stem vessel obliteration: there is marked thickening of the vessel wall with resultant obliteration of the vascular lumen (hematoxylin-eosin, original magnification ×10).*

Figure 27. *Vascular ectasia: the luminal diameter of the chorionic vessel is more than four times that of the adjacent vessels (hematoxylin-eosin, original magnification ×2).*

Figure 28. *Term placenta showing delayed villous maturation: there is a monotonous villous population of villi with centrally placed capillaries and decreased vasculosyncytial membranes (hematoxylin-eosin, original magnification ×4).*

Figure 29. *Neutrophils in the subchorial intervillous space, in itself indicating subchorionitis (hematoxylin-eosin, original magnification ×10).*

Staging and Grading of the Maternal and Fetal Inflammatory Responses in Ascending Intrauterine Infection	
Maternal Inflammatory Response	
Stage 1—acute subchorionitis or chorionitis Stage 2—acute chorioamnionitis: polymorphonuclear leukocytes extend into fibrous chorion and/or amnion Stage 3—necrotizing chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia	Grade 1—not severe as defined Grade 2—severe: confluent polymorphonuclear leukocytes or with subchorionic microabscesses
Fetal Inflammatory Response	
Stage 1—chorionic vasculitis or umbilical phlebitis Stage 2—involvement of the umbilical vein and one or more umbilical arteries Stage 3—necrotizing funisitis	Grade 1—not severe as defined Grade 2—severe: near-confluent intramural polymorphonuclear leukocytes with attenuation of vascular smooth muscle

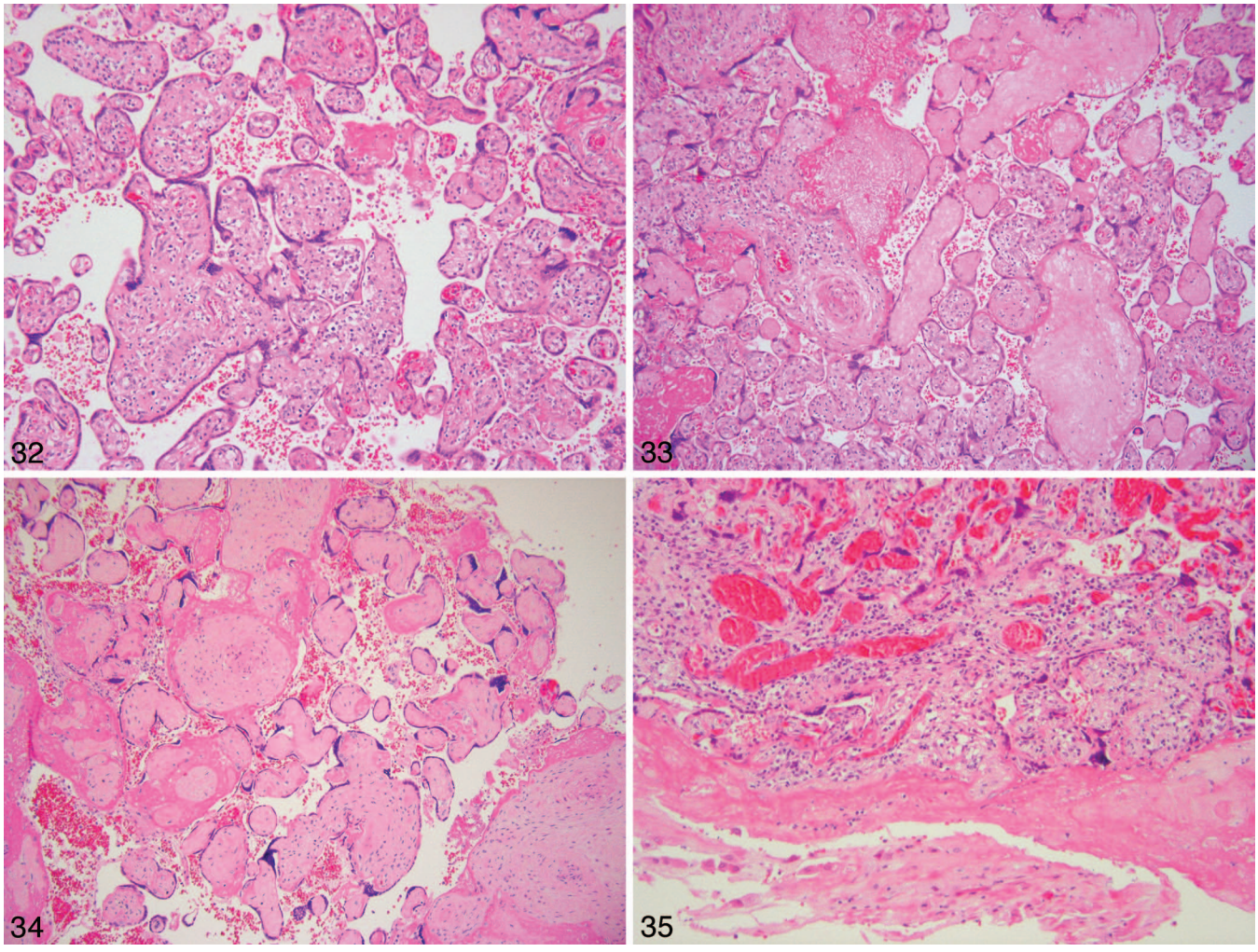


Figure 32. *High-grade villitis of unknown etiology: this focus affects more than 10 contiguous villi (hematoxylin-eosin, original magnification ×10).*

Figure 33. *Occasional avascular villi with scattered inflammatory cells suggesting "burnt-out villitis" (hematoxylin-eosin, original magnification ×10).*

Figure 34. *Contiguous, uniformly hyalinized, avascular villi suggesting upstream vascular occlusion (hematoxylin-eosin, original magnification ×4).*

Figure 35. *Bandlike parabasal villitis (hematoxylin-eosin, original magnification ×10).*

←

Figure 30. *Acute inflammation extending beyond the chorion laeve layer into the amnion, indicating acute chorioamnionitis (hematoxylin-eosin, original magnification ×10).*

Figure 31. *Low-grade villitis of unknown etiology: there is inflammation affecting a group of more than 5 contiguous villi (hematoxylin-eosin, original magnification ×20).*

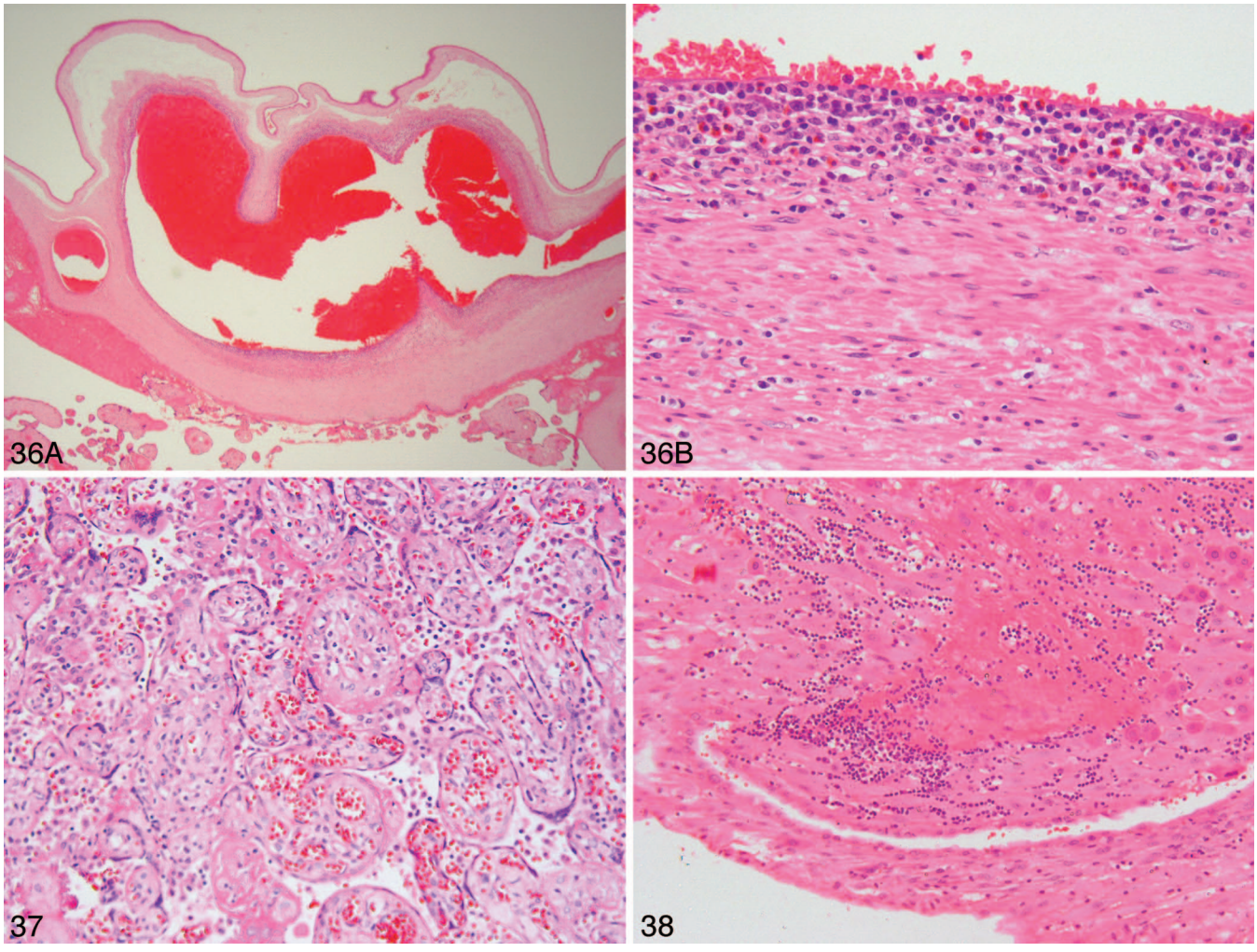


Figure 36. *A, Eosinophilic/T-cell vasculitis in a chorionic plate vessel. B, High-power view shows a mixture of T lymphocytes and eosinophils (hematoxylin-eosin, original magnifications ×2 [A] and ×40 [B]).*

Figure 37. *Chronic intervillositis: infiltration of the intervillous space by histiocytes (hematoxylin-eosin, original magnification ×20).*

Figure 38. *Chronic deciduitis: a heavy infiltration of lymphocytes and plasma cells is seen in the basal plate (hematoxylin-eosin, original magnification ×20).*

have been reported in neonates with umbilical arteritis compared with those without.[64]

Reporting Format.—Based on our current understanding of the disease process, it is recommended that histologic acute inflammation in the placenta, extraplacental membranes, and umbilical cord be reported as: acute chorioamnionitis (or acute chorionitis) with/without fetal inflammatory response in (specify) chorionic vessels, umbilical vein, and/or umbilical artery (or arteries).

Some pathologists may prefer to use the terms *maternal inflammatory response* and *fetal inflammatory response*.

Villitis of Unknown Etiology

Villitis of unknown etiology (synonymous with villitis of unknown aetiology) is a histologic diagnosis and, although it may have a variable distribution, evidence indicates that 3 parenchymal blocks will identify 62% of villitis, reaching an asymptote of 6 and 7 blocks identifying 85% of villitis.[37] Villitis of unknown etiology by definition excludes those cases where an etiology is identified, such as viral or acute infections, and thus is preferred to the term *nonspecific chronic villitis*. It is usually lymphohistiocytic: although the presence of rare plasma cells does not exclude the diagnosis, thorough evaluation for an infectious etiology, such as cytomegalovirus, is required in a predominantly plasma cell villitis.

Grading Schema.—Where villitis of unknown etiology is diagnosed, it should be graded as low grade or high grade. Low grade is defined as the presence of inflammation affecting fewer than 10 contiguous villi in any one focus (Figure 31), with more than one focus required for the diagnosis. High grade is defined as the presence of multiple foci, on more than one section, at least one of which shows inflammation affecting more than 10 contiguous villi (Figure 32).

Distinguishing between low-grade and high-grade villitis is important because there are significant associations between the latter and FGR, neurodevelopmental impairment, and likelihood of recurrence.[66]

Low-grade lesions should be further classified as focal when they are seen in one slide, all foci affecting fewer than 10 villi, with more than one focus required for diagnosis; or

as multifocal when they are present in more than one slide, all foci affecting fewer than 10 contiguous villi. High-grade lesions should be further classified as patchy when there are multiple foci, with at least one focus with 10 or more contiguous villi, and seen in one or more slides; or as diffuse when more than 30% of all distal villi are involved.

Rarely, a single focus of affected villi is seen. In the absence of any evidence at present, when the single focus is small (<10 affected villi) it should be reported as "ungradable–possible low grade," and when the single focus contains 10 or more affected villi it should be reported as "ungradable–possible high grade."

Vascular Damage.—When inflammatory cells damage vessels that have a muscular wall, the term *villitis with stem vessel obliteration* should be used. When avascular villi are seen in a placenta with villitis, the report should designate the finding as *chronic villitis with associated avascular villi*.

Villitis may cause impairment of the fetoplacental circulation. Such damage is associated with adverse effects, such as neurologic impairment.[67]

Although occasional avascular villi with scattered inflammatory cells (Figure 33) may indicate "burnt-out villitis," and large areas of contiguous, uniformly hyalinized, avascular villi (Figure 34) may suggest upstream vascular occlusion, it can be difficult to ascribe the avascular villi to either the inflammatory or the obstructive process.

Location.—When possible, the distribution of the foci of villitis should be reported as being located parabasal/paraseptal, randomly in the midparenchyma or subchorionic zone, or combinations thereof.

Parabasal and basal villitis is often associated with chronic deciduitis and is reportedly seen more frequently in pregnancies from assisted reproductive technology, especially ovum-donor conceptions,[68] with implications for the understanding of aberrant maternofetal immunologic interplay (Figure 35). Documenting the distribution, together with the extent (grade) of villitis may further our understanding of the lesion and its clinical associations.

Other Inflammatory Lesions.—Entities reported to be associated with villitis, such as eosinophilic/T-cell vasculitis, chronic intervillositis, and chronic deciduitis, should be noted.

Eosinophilic/T-cell vasculitis may occur on either aspect of a chorionic plate vessel, and it consists of T lymphocytes accompanied by eosinophils, with occasional associated thrombosis (Figure 36).[69–71] Chronic intervillositis can be associated with adverse pregnancy outcomes and can be recurrent. Cases with villitis have been specifically excluded,[72,73] but others have described their co-occurrence (Figure 37).[74,75] Chronic deciduitis can be defined by the extent of chronic inflammation, and the presence of plasma cells, within the basal plate (Figure 38).[76]

COMMENT AND FUTURE PERSPECTIVES

The workshop reached consensus regarding a broad set of conclusions.

Although the impetus for the consensus workshop stemmed from the uncertainty about the contribution of placental pathology to the cause of stillbirth arising from variability in sampling and definitions, the workshop participants were cognizant that the guidelines reached at the meeting were applicable to the reporting of placentas in the setting of surgical pathology, whether in tertiary centers or in community hospitals and district general hospitals. It also needed to be relevant to the scientific research community.[77]

The group did not explore in detail different grading schemes that were in use for some lesions, such as villitis of unknown etiology, but did recommend ones that were most commonly used and that had the most weight of evidence supporting their use.

For some lesions where threshold levels have been in use previously, such as infarction, it was thought advisable to document their size/volume. For other lesions, such as delayed villous maturation, more information is needed to refine threshold levels.

Following the meeting, the group considered the need to define critical values in placental pathology. In most cases, the relevance of the findings or their absence can change as clinical information emerges. Some lesions, such as chronic intervillositis, high-grade villitis of unknown etiology, and maternal floor infarction, are important by virtue of their high recurrence risk and their association with adverse pregnancy outcomes. They merit communication to the clinicians, although not necessarily as findings that demand immediate interventions, which the term "critical values" may imply.

The group acknowledged that not every pathologist, physician, or scientist with an interest in placental pathology could attend the workshop. Nevertheless, we had sought as wide a participatory group as was possible, and we encouraged those who could attend to discuss widely with their colleagues prior to the meeting, and those who could not attend to comment on the issues. It is highly likely that a further update consensus workshop may be necessary as developments in our understanding of the pathology of the placenta, its scientific basis, and the clinical significance of these defined lesions evolve.

The workshop attendees were aware that as clinical management evolves and our understanding of the pathophysiology of placenta advances, these definitions, with their grading, may need to be revised. For example, just as it has been recommended that the definition of "term" pregnancy be changed to reflect the differences in neonatal outcome between early, full, and late term,[78] it is likely that refinement in definitions may allow closer clinicopathologic correlations.

We thank the Academic Medical Center, Amsterdam, for hosting the workshop, and the Scientific Committee, International Stillbirth Alliance, for providing the impetus for the workshop.

References

1. Lawn J, Shibuya K, Stein C. No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. *Bull World Health Organ*. 2005;83(6):409–417.

2. Lawn JE, Blencowe H, Pattinson R, et al. Stillbirths: Where? When? Why? How to make the data count? *Lancet*. 2011;377(9775):1448–1463.

3. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. *Placenta*. 2014;35(8):552–562.

4. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. *Arch Pathol Lab Med*. 1997;121(5):449–476.

5. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2004;7(5):443–452.

6. Redline RW, Boyd T, Campbell V, et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2004;7(3):237–249.

7. Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C; Amniotic Fluid Infection Nosology Committee Society for Pediatric Pathology Perinatal Section. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2003;6(5):435–448.

8. Roland MC, Friis CM, Voldner N, et al. Fetal growth versus birthweight: the role of placenta versus other determinants. *PLoS One*. 2012;7(6):e39324.

9. Molteni RA, Stys SJ, Battaglia FC. Relationship of fetal and placental weight in human beings: fetal/placental weight ratios at various gestational ages and birth weight distribution. *J Reprod Med*. 1978;21(5):327–334.
10. Fox GE, Van Wesep R, Resau JH, Sun CCJ. The effect of immersion formaldehyde fixation on human placental weight. *Arch Pathol Lab Med*. 1991; 115(7):726–728.
11. Barker DJ, Osmond C, Thornburg KL, Kajantie E, Eriksson JG. The lifespan of men and the shape of their placental surface at birth. *Placenta*. 2011;32(10): 783–787.
12. Barker DJ, Osmond C, Thornburg KL, Kajantie E, Eriksson JG. The shape of the placental surface at birth and colorectal cancer in later life. *Am J Hum Biol*. 2013;25(4):566–568.
13. Eriksson JG, Kajantie E, Thornburg KL, Osmond C, Barker DJ. Mother's body size and placental size predict coronary heart disease in men. *Eur Heart J*. 2011;32(18):2297–2303.
14. Longtine MS, Nelson DM. Placental dysfunction and fetal programming: the importance of placental size, shape, histopathology, and molecular composition. *Semin Reprod Med*. 2011;29(3):187–196.
15. Misra DP, Salafia CM, Charles AK, Miller RK. Placental measurements associated with intelligence quotient at age 7 years. *J Dev Orig Health Dis*. 2012; 3(3):190–197.
16. Thornburg K, O'Tierney P, Louey S. The placenta is a programming agent for cardiovascular disease. *Placenta*. 2010;31(suppl):S54–S59.
17. Winder NR, Krishnaveni GV, Veena SR, et al. Mother's lifetime nutrition and the size, shape and efficiency of the placenta. *Placenta*. 2011;32(11):806–810.
18. Warrander LK, Batra G, Bernatavicius G, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PLoS One*. 2012;7(4):e34851.
19. Cromi A, Ghezzi F, Di Naro E, Siesto G, Bergamini V, Raio L. Large cross-sectional area of the umbilical cord as a predictor of fetal macrosomia. *Ultrasound Obstet Gynecol*. 2007;30(6):861–866.
20. Proctor LK, Fitzgerald B, Whittle WL, et al. Umbilical cord diameter percentile curves and their correlation to birth weight and placental pathology. *Placenta*. 2013;34(1):62–66.
21. Raio L, Ghezzi F, Di Naro E, Duwe DG, Cromi A, Schneider H. Umbilical cord morphologic characteristics and umbilical artery Doppler parameters in intrauterine growth-restricted fetuses. *J Ultrasound Med*. 2003;22(12):1341–1347.
22. Baergen RN, Malicki D, Behling C, Benirschke K. Morbidity, mortality, and placental pathology in excessively long umbilical cords: retrospective study. *Pediatr Dev Pathol*. 2001;4(2):144–153.
23. Georgiadis L, Keski-Nisula L, Harju M, et al. Umbilical cord length in singleton gestations: a Finnish population-based retrospective register study. *Placenta*. 2014;35(4):275–280.
24. Krakowiak P, Smith EN, de Bruyn G, Lydon-Rochelle MT. Risk factors and outcomes associated with a short umbilical cord. *Obstet Gynecol*. 2004;103(1): 119–127.
25. Moessinger AC, Blanc WA, Marone PA, Polsen DC. Umbilical cord length as an index of fetal activity: experimental study and clinical implications. *Pediatr Res*. 1982;16(2):109–112.
26. Naeye RL. Umbilical cord length: clinical significance. *J Pediatr*. 1985; 107(2):278–281.
27. Di Salvo DN, Benson CB, Laing FC, Brown DL, Frates MC, Doubilet PM. Sonographic evaluation of the placental cord insertion site. *AJR Am J Roentgenol*. 1998;170(5):1295–1298.
28. Luo G, Redline RW. Peripheral insertion of umbilical cord. *Pediatr Dev Pathol*. 2013;16(6):399–404.
29. de Laat MW, Franx A, Bots ML, Visser GH, Nikkels PG. Umbilical coiling index in normal and complicated pregnancies. *Obstet Gynecol*. 2006;107(5): 1049–1055.
30. de Laat MWM, van Alderen ED, Franx A, Visser GHA, Bots ML, Nikkels PGJ. The umbilical coiling index in complicated pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2007;130(1):66–72.
31. Jessop FA, Lees CC, Pathak S, Hook CE, Sebire NJ. Umbilical cord coiling: clinical outcomes in an unselected population and systematic review. *Virchows Arch*. 2014;464(1):105–112.
32. van Diik CC, Franx A, de Laat MW, Bruinse HW, Visser GH, Nikkels PG. The umbilical coiling index in normal pregnancy. *J Matern Fetal Neonatal Med*. 2002;11(4):280–283.
33. Khong TY. Evidence-based pathology: umbilical cord coiling. *Pathology*. 2010;42(7):618–622.
34. Downey A, Hore K, McAuliffe FM, Mooney E. Umbilical cord shortening: quantification post-delivery and post-fixation. *Pediatr Dev Pathol*. 2014;17(5): 327–329.
35. Ernst LM, Minturn L, Huang MH, Curry E, Su EJ. Gross patterns of umbilical cord coiling: correlations with placental histology and stillbirth. *Placenta*. 2013; 34(7):583–588.
36. Redline RW, Wilson-Costello D. Chronic peripheral separation of placenta: the significance of diffuse chorioamnionic hemosiderosis. *Am J Clin Pathol*. 1999; 111(6):804–810.
37. Altemani A, Gonzatti A, Metze K. How many paraffin blocks are necessary to detect villitis? *Placenta*. 2003;24(1):116–117.
38. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol*. 1986;93(10): 1049–1059.
39. Hempstock J, Jauniaux E, Greenwold N, Burton GJ. The contribution of placental oxidative stress to early pregnancy failure. *Hum Pathol*. 2003;34(12): 1265–1275.
40. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. *Am J Pathol*. 2003;162(1):115–125.
41. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta*. 2009;30(6):473–482.
42. Bendon RW. Nosology: infarction hematoma, a placental infarction encasing a hematoma. *Hum Pathol*. 2012;43(5):761–763.
43. Veerbeek JHW, Nikkels PGJ, Torrance HL, et al. Placental pathology in early intrauterine growth restriction associated with maternal hypertension. *Placenta*. 2014;35(9):696–701.
44. Loukeris K, Sela R, Baergen RN. Syncytial knots as a reflection of placental maturity: reference values for 20 to 40 weeks' gestational age. *Pediatr Dev Pathol*. 2010;13(4):305–309.
45. Morgan TK, Tolosa JE, Mele L, et al. Placental villous hypermaturation is associated with idiopathic preterm birth. *J Matern Fetal Neonatal Med*. 2013; 26(7):647–653.
46. Goldenberg RL, Faye-Petersen O, Andrews WW, Goepfert AR, Cliver SP, Hauth JC. The Alabama Preterm Birth Study: diffuse decidual leukocytoclastic necrosis of the decidua basalis, a placental lesion associated with preeclampsia, indicated preterm birth and decreased fetal growth. *J Matern Fetal Neonatal Med*. 2007;20(5):391–395.
47. Stanek J, Al-Ahmadie HA. Laminar necrosis of placental membranes: a histologic sign of uteroplacental hypoxia. *Pediatr Dev Pathol*. 2005;8(1):34–42.
48. Stanek J, Weng E. Microscopic chorionic pseudocysts in placental membranes: a histologic lesion of in utero hypoxia. *Pediatr Dev Pathol*. 2007; 10(3):192–198.
49. Bendon RW, Coventry SC, Reed RC. Reassessing the clinical significance of chorionic membrane microcysts and linear necrosis. *Pediatr Dev Pathol*. 2012; 15(3):213–216.
50. Chisholm KM, Heerema-McKenney A. Fetal thrombotic vasculopathy: significance in liveborn children using proposed Society for Pediatric Pathology diagnostic criteria. *Am J Surg Pathol*. 2015;39(2):274–280.
51. Lepais L, Gaillot-Durand L, Boutitie F, et al. Fetal thrombotic vasculopathy is associated with thromboembolic events and adverse perinatal outcome but not with neurologic complications: a retrospective cohort study of 54 cases with a 3-year follow-up of children. *Placenta*. 2014;35(8):611–617.
52. Tantbirojn P, Saleemuddin A, Sirois K, et al. Gross abnormalities of the umbilical cord: related placental histology and clinical significance. *Placenta*. 2009;30(12):1083–1088.
53. Redline RW. Clinical and pathological umbilical cord abnormalities in fetal thrombotic vasculopathy. *Hum Pathol*. 2004;35(12):1494–1498.
54. Beeksma FA, Erwich JJHM, Khong TY. Placental fetal vascular thrombosis lesions and maternal thrombophilia. *Pathology*. 2012;44(1):24–28.
55. Parast MM, Crum CP, Boyd TK. Placental histologic criteria for umbilical blood flow restriction in unexplained stillbirth. *Hum Pathol*. 2008;39(6):948–953.
56. Cooley SM, Donnelly JC, Walsh T, Kirkham C, Gillan J, Geary MP. Ponderal index (PI) vs birth weight centiles in the low-risk primigravid population: which is the better predictor of fetal wellbeing? *J Obstet Gynaecol*. 2012;32(5): 439–443.
57. Evers IM, Nikkels PG, Sikkema JM, Visser GH. Placental pathology in women with type 1 diabetes and in a control group with normal and large-for-gestational-age infants. *Placenta*. 2003;24(8–9):819–825.
58. Higgins M, McAuliffe FM, Mooney EE. Clinical associations with a placental diagnosis of delayed villous maturation: a retrospective study. *Pediatr Dev Pathol*. 2011;14(4):273–279.
59. Stallmach T, Hebisch G, Meier K, Dudenhausen JW, Vogel M. Rescue by birth: defective placental maturation and late fetal mortality. *Obstet Gynecol*. 2001;97(4):505–509.
60. Been JV, Lievense S, Zimmermann LJ, Kramer BW, Wolfs TG. Chorioamnionitis as a risk factor for necrotizing enterocolitis: a systematic review and meta-analysis. *J Pediatr*. 2013;162(2):236–242.e2.
61. Chen ML, Allred EN, Hecht JL, et al. Placenta microbiology and histology and the risk for severe retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2011;52(10):7052–7058.
62. Jones MH, Corso AL, Tepper RS, et al. Chorioamnionitis and subsequent lung function in preterm infants. *PLoS One*. 2013;8(12):e81193.
63. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy. *JAMA*. 2000;284(11):1417–1424.
64. Kim CJ, Yoon BH, Romero R, et al. Umbilical arteritis and phlebitis mark different stages of the fetal inflammatory response. Am J Obstet Gynecol 2001; 185(2): 496–500.
65. Rogers BB, Alexander JM, Head J, McIntire D, Leveno KJ. Umbilical vein interleukin-6 levels correlate with the severity of placental inflammation and gestational age. *Hum Pathol*. 2002;33(3):335–340.
66. Tamblyn JA, Lissauer DM, Powell R, Cox P, Kilby MD. The immunological basis of villitis of unknown etiology - review. *Placenta*. 2013;34(10):846–855.

67. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. *Am J Obstet Gynecol*. 2005;192(2):452–457.

68. Styer AK, Parker HJ, Roberts DJ, Palmer-Toy D, Toth TL, Ecker JL. Placental villitis of unclear etiology during ovum donor in vitro fertilization pregnancy. *Am J Obstet Gynecol*. 2003;189(4):1184–1186.

69. Fraser RB, Wright JR Jr. Eosinophilic/T-cell chorionic vasculitis. *Pediatr Dev Pathol*. 2002;5(4):350–355.

70. Jacques SM, Qureshi F, Kim CJ, et al. Eosinophilic/T-cell chorionic vasculitis: a clinicopathologic and immunohistochemical study of 51 cases. *Pediatr Dev Pathol*. 2011;14(3):198–205.

71. Katzman PJ, Oble DA. Eosinophilic/T-cell chorionic vasculitis and chronic villitis involve regulatory T cells and often occur together. *Pediatr Dev Pathol*. 2013;16(4):278–291.

72. Boyd TK, Redline RW. Chronic histiocytic intervillositis: a placental lesion associated with recurrent reproductive loss. *Hum Pathol*. 2000;31(11):1389–1396.

73. Marchaudon V, Devisme L, Petit S, Ansart-Franquet H, Vaast P, Subtil D. Chronic histiocytic intervillositis of unknown etiology: clinical features in a consecutive series of 69 cases. *Placenta*. 2011;32(2):140–145.

74. Contro E, deSouza R, Bhide A. Chronic intervillositis of the placenta: a systematic review. *Placenta*. 2010;31(12):1106–1110.

75. Jacques SM, Qureshi F. Chronic intervillositis of the placenta. *Arch Pathol Lab Med*. 1993;117(10):1032–1035.

76. Khong TY, Bendon RW, Qureshi F, et al. Chronic deciduitis in the placental basal plate: definition and interobserver reliability. *Hum Pathol*. 2000;31(3):292–295.

77. Barbaux S, Erwich JJ, Favaron PO, et al. IFPA meeting 2014 workshop report: animal models to study pregnancy pathologies; new approaches to study human placental exposure to xenobiotics; biomarkers of pregnancy pathologies; placental genetics and epigenetics; the placenta and stillbirth and fetal growth restriction. *Placenta*. 2015;36(suppl 1):S5–S10.

78. Spong CY. Defining "term" pregnancy: recommendations from the Defining "Term" Pregnancy Workshop. *JAMA*. 2013;309(23):2445–2446.