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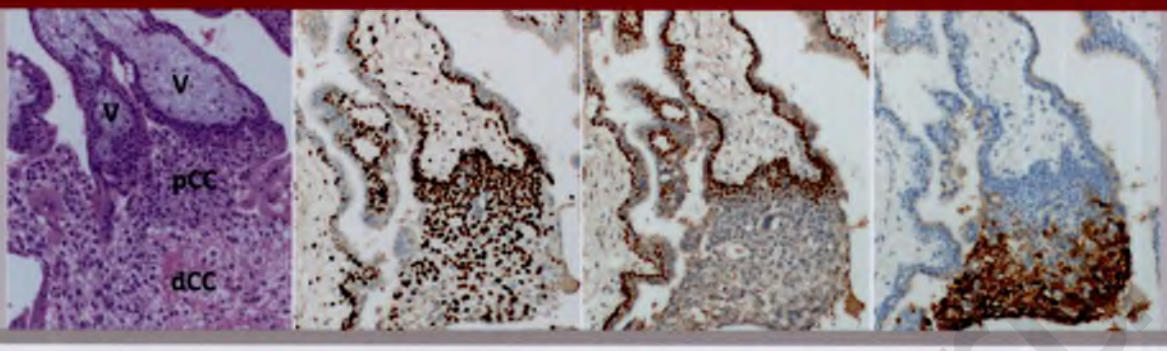

Placental and Gestational Pathology

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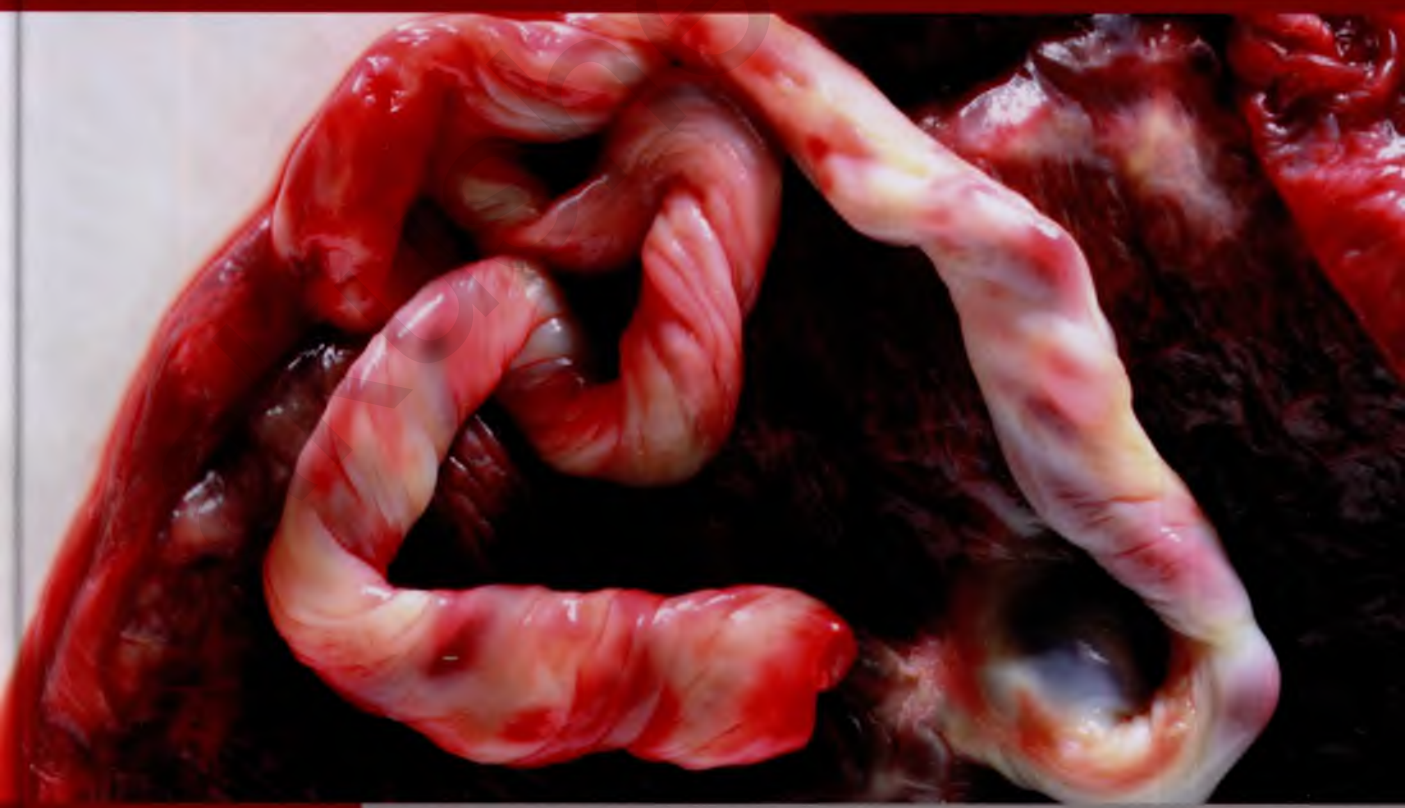

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Placental and Gestational Pathology

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Preface

Interest in the critical role that the placenta plays in pregnancy disorders and the subsequent health of both mother and child has dramatically accelerated. Seminal concepts including the fetal origins of adult disease (David Barker) and the role of evolutionary maternal-fetal conflicts in pregnancy outcomes (David Haig) combined with unprecedented advances in fetal imaging, biochemical monitoring, and genomic analyses have coalesced to properly identify the placenta as a central orchestrator of successful pregnancy outcomes.

Pathology is widely recognized as the critical link between abnormal pathophysiology, clinical disease, and adverse outcomes in other organ systems. Yet placental pathology has lingered for many years as an understudied, underappreciated, and esoteric sideshow largely ignored by basic scientists and clinicians. This is no longer true. A diagnostic framework has been established, reproducibility has been demonstrated, and uniform diagnostic criteria and nomenclature for common lesions have been disseminated by the Amsterdam International Consensus Group. Continuing meetings of this group have been planned to complete these tasks for less common processes. Efforts in the US, such as the NIH Human Placenta Project and the NICHD Placenta Atlas Tool, and large studies around the world now all include a rigorous assessment of placental pathology.

The purpose of this book is to present a comprehensive overview of the new international consensus framework for placental pathology using a concise descriptive format that provides preferred nomenclature, alternative terms, definitions, proposed pathogenesis, clinical correlation, gross and microscopic features, prognostic implications, key references, and illustrative examples for every lesion. In addition to its focus on new terminology and its very specific outlined format, this book varies from other placental pathology textbooks by including comprehensive coverage of early pregnancy pathology and the pathology of the surrounding gravid uterus, and how they relate to findings in later placentas and overall pregnancy outcome.

We anticipate that this book will be of use to pathologists at all stages of training and practice ranging from first-year residents to subspecialty pediatric and perinatal pathologists. Pathologists in training will appreciate the concise descriptions and illustrations of each lesion. Experienced pathologists will find it useful to have the latest information for each lesion and will appreciate the unique insights provided by individual chapter authors, each of whom is not only a recognized expert in placental pathology in general but has also published widely on his or her individual chapter topic. We also strongly believe that this book will be of use to clinicians, including obstetricians ranging from general practitioners to maternal fetal medicine specialists, neonatologists, child neurologists, and clinical geneticists, and to basic scientists interested in development, perinatal physiology, and the gestational origins of childhood and adult diseases.

Finally, the impetus for this textbook and our underlying approach to placental pathology can be largely attributed to Dr. Shirley Driscoll, and we dedicate this book to her. Her vast experience in gestational pathology was imbued either directly or indirectly to us through our training and experiences in the Women's and Perinatal Pathology Division of the Brigham and Women's Hospital from 1985 to the present. Although Shirley retired from clinical practice in 1989, the principles she established, working in concert with other outstanding pathologists such as Arthur Hertig and Kurt Benirschke, have guided each of us throughout our subsequent careers and are responsible for any success we have had in moving the field forward.

Chapter 1

Normal Development

Mana Parast

Early Development of the Placenta

Development of the placenta begins with cavitation of the morula, the compact sphere of cells, and transitions to the blastocyst stage of embryonic development. At this stage, the first lineage segregation takes place, with a single layer of cells on the outer part of the blastocyst forming the trophectoderm (TE), the precursor to trophoblast, the epithelial cells of the placenta[1]. Cells remaining in the middle of the blastocyst are referred to as the inner cell mass (ICM), which gives rise to all embryonic structures, as well as some extraembryonic structures (see below). TE cells have tight junctions, which are required for fluid accumulation within the blastocoel cavity. Unlike cells in the ICM, TE cells are also characterized by apico-basal polarity, a process that sets into motion signals leading to trophoblast lineage specification[1].

Once formed, the polar TE (cells nearest to the ICM) is responsible for attachment to the endometrium. Attachment is rapidly followed by invasion of the blastocyst into and below the uterine lining. Once embedded within the endometrium, the TE rapidly expands, giving rise to two cell populations: a mononuclear cytotrophoblast (CTB) and a multinucleated syncytium. The latter secretes enzymes that degrade the surrounding tissue and also tap into maternal sinusoids, finally giving rise to blood-filled lacunae that are lined by this syncytium. In the meantime, the mononuclear CTBs proliferate, forming a shell around the implanted blastocyst[2] (Figure 1.1a). Invaginations of CTB within this shell begin the formation of primary villi, while the invasion of these structures with mesenchymal cells leads to the formation of secondary villi (Figure 1.1b).

Cytotrophoblast as the Trophoblast Stem Cell

Akin to stem cells in other stratified epithelia, such as skin, the cytotrophoblast (CTB) reside adjacent to villous stroma and sit atop a basement membrane. Similar to stem cells in these other organs, CTB

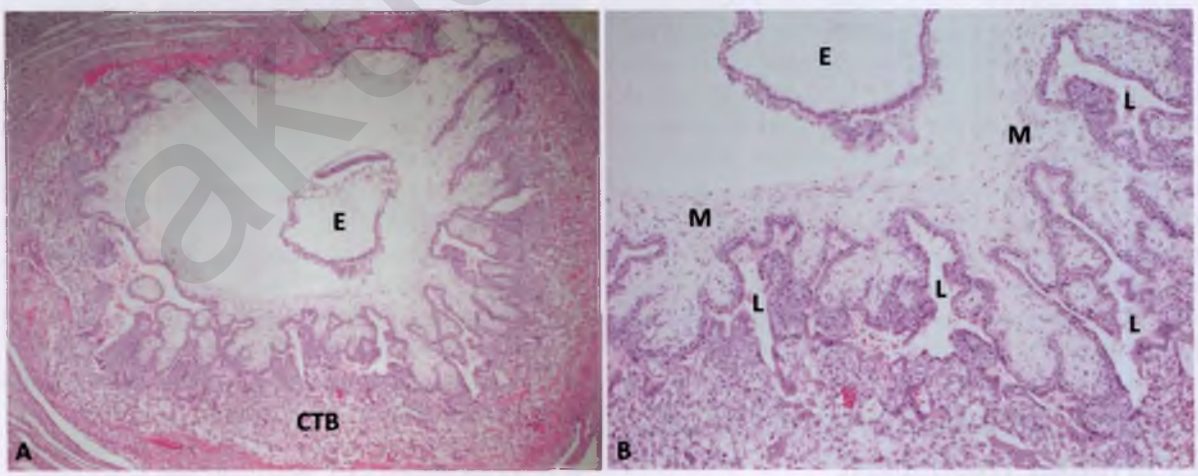

Figure 1.1 Cross-section through a 4-week gestational age embryo. (a) Placenta (the cytotrophoblastic shell, or CTB) makes up a much greater proportion of tissue compared to the embryo-proper (E). (b) Secondary villi containing mesenchyme (M) surround lacunae (L) containing maternal blood.

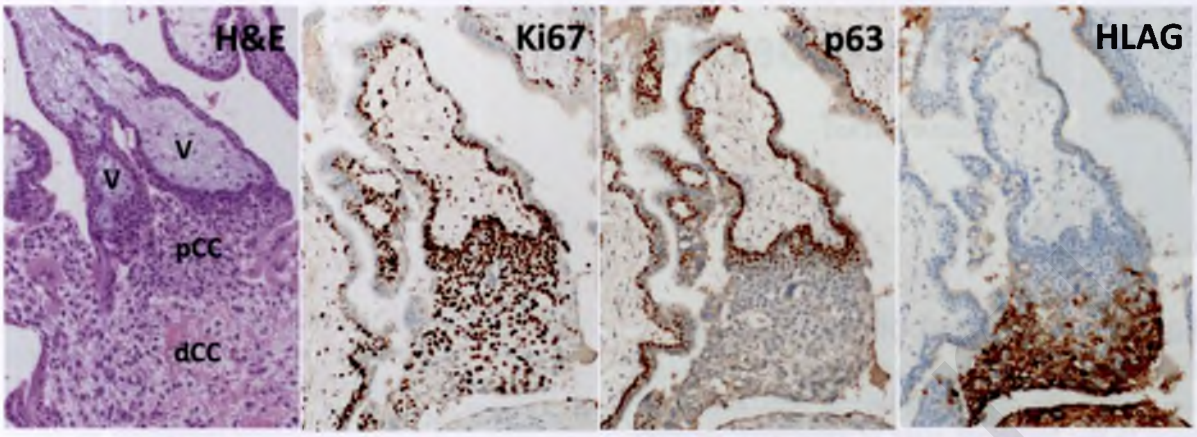

Figure 1.2 Early (8-week gestational age) implantation site. Anchoring villi (V) with trophoblast cell columns (CC) growing toward the uterine wall. The proximal CC (pCC) consists of $p63^{+}/Ki67^{+}$ cells, which are gradually lost in the distal CC (dCC), containing mature EVT which express HLA-G, among other markers.

express the N-terminal truncated isoform of p63 (ΔNp63), an oncogene and member of the p53 nuclear protein family, which is lost quickly upon differentiation of CTB, as they move away from the underlying villous stroma[3]. Other markers expressed in CTB include membrane proteins E-Cadherin, EGFR, and integrins alpha-6 and beta-4; as they are proliferative cells, they also express Ki67[4].

Whether the proliferating CTB layer, or the TE from which it arose, contains true trophoblast stem cells (TSC) – cells which can give rise to all trophoblast subtypes – is not known. Unlike mouse TSC, which have been derived from both pre-implantation blastocysts and post-implantation extraembryonic tissues[5], human TSC have yet to be characterized or derived[6]. While there is not a clear consensus, data point to the early post-implantation villous placenta as the most likely niche for human TSC[6]. In addition to p63, at least a subset of CTB in 5–8 week gestation placentae also express CDX2, a homeobox-domain containing transcription factor, which defines TSC in mice; this CTB subset greatly diminishes by the end of the first trimester[7]. Nevertheless, isolation and further characterization of this subpopulation, including its capacity to differentiate into all trophoblast subtypes ("multipotency"), have yet to be evaluated.

Implantation and Differentiation of Extravillous Trophoblast

At the basal plate, anchoring chorionic villi extend cell columns towards the uterus, which serve to firmly attach the feto-placental unit to maternal tissues. At the proximal portion of the cell column, trophoblast proliferate, differentiating from CTB into extravillous trophoblast (EVT) as they move further away from the mesenchymal villous core (Figure 1.2). This transition is accompanied by changes in gene expression, including loss of p63, and gain of other transcription factors such as ASCL2. There are also changes in membrane protein expression, with loss of E-Cadherin, EGFR, and integrins alpha-6 and beta-4; and gain of MelCAM, the nonclassical histocompatibility antigens HLA-G, HLA-C, and HLA-E, and integrins alpha-5 and beta-1 (Figure 1.2)[3][4]. As the cells approach the uterine wall, they lose their tight epithelial morphology and begin to dissociate from the column, developing more elongated and mesenchymal morphology and gaining invasive potential. Distal cell column and mature EVT at the implantation site are characterized by integrins alpha-1 and beta-1; they retain expression of HLA-G and MelCAM[4].

Mature EVT invade the uterine wall, either staying within the decidua or myometrium as interstitial EVT, or remodeling maternal vessels as endovascular EVT. Most mature EVT are mononuclear, though binucleate and multinucleate forms can occur (Figure 1.3a–b). EVT nuclei often appear irregular with prominent nucleoli and are surrounded by abundant eosinophilic-to-amphophilic cytoplasm. As these cells are fully differentiated, mitotic forms are rare. As interstitial EVT, these cells invade the uterine wall, singly or in groups, extending into the inner third of the myometrium. As endovascular EVT,

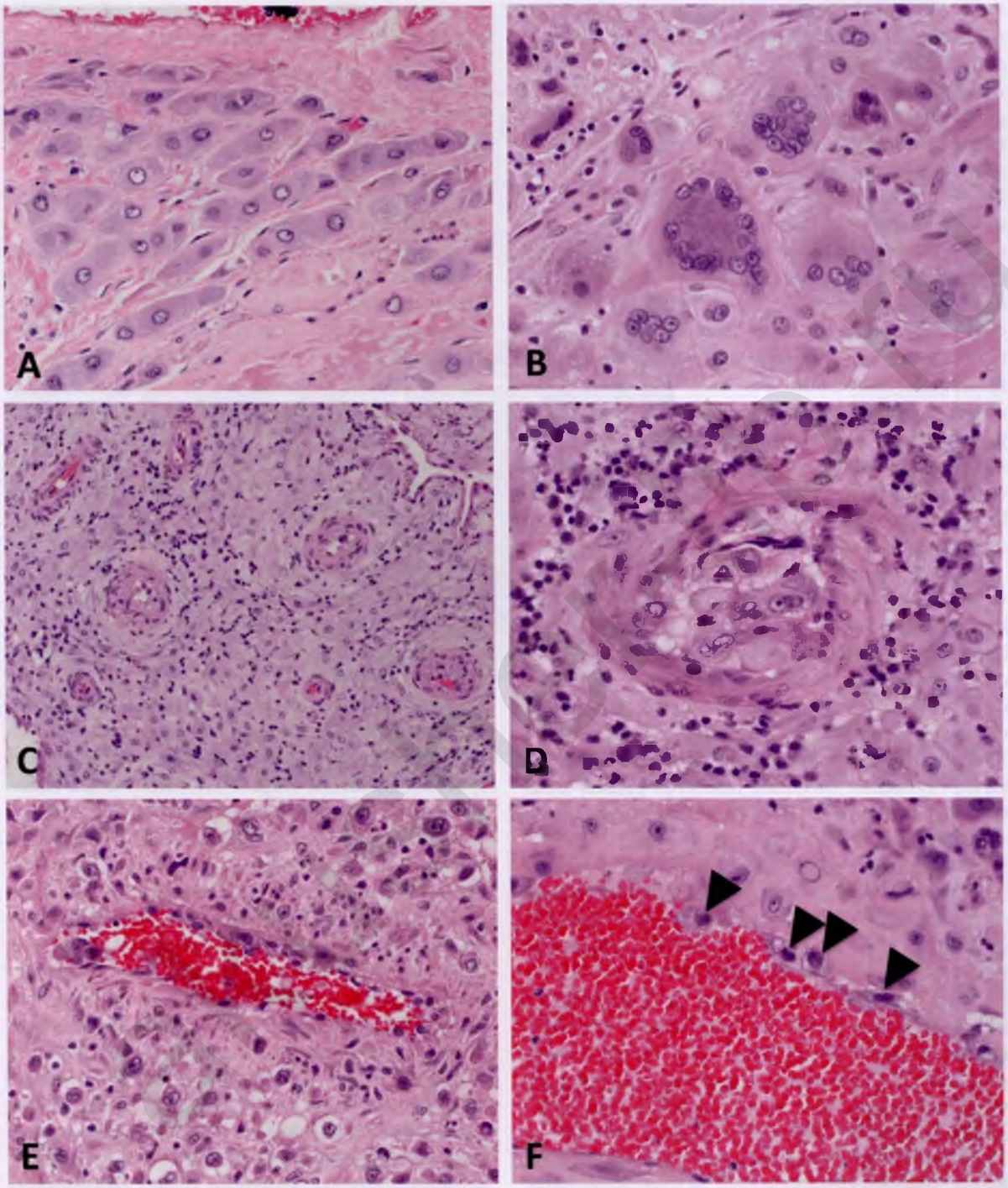

Figure 1.3 EVT at the implantation site. Interstitial EVT can be either (a) mononuclear or (b) multinucleated. Endovascular EVT invade and remodel maternal spiral arterioles: (c) shows arterioles prior to remodeling, (d) an arteriole with an EVT "plug," and (e) a vessel in process of remodeling, still retaining some smooth muscle in its wall. In (f), the remodeled vessel is lined by endovascular EVT (arrowheads).

they initially plug maternal spiral arterioles, then migrate and remodel these vessels, replacing maternal endothelium (Figure 1.3c–d). During this process, referred to as "physiologic conversion" or "physiologic change," maternal spiral arterioles are transformed from high-resistance, low-capacitance vessels to low-resistance, high-capacitance vessels (compare Figure 1.3c to 1.3e–f). As a result of this conversion, these maternal vessels lose the ability to respond to maternal systemic blood pressure and instead continuously deliver a large percentage of maternal cardiac output toward the placenta[4]. This process is vital to the continuous growth and development of the placenta (and therefore the fetus). Abnormal or incomplete conversion has been associated with a wide range of pregnancy complications, including preeclampsia, fetal growth restriction (FGR), and recurrent miscarriage. Recent data, however, point to re-endothelialization of the maternal arterioles following physiologic conversion; the consequences of this process are as yet unclear[4].

During the implantation process, EVT interact with the maternal immune cells in the decidua, including macrophages and natural killer (NK) cells. Both of these cell populations are distinct from the respective cells at other sites, based on both marker expression and function, and hence are referred to as decidual/uterine macrophages and NK cells. Cross talk between EVT and decidual immune cells leads to secretion of various cytokines, including interferon-gamma from the latter cells, which modulates EVT invasion and regulates the physiologic conversion process[8]. These interactions are vital to implantation, as lack of decidua (and thus the decidual immune cells) leads to invasive placentation (i.e. either in intrauterine pregnancy as in cases of placenta accreta, or extrauterine pregnancy as implantation within the Fallopian tube)[4].

More recently, another group of immune cells, namely regulatory T cells, has been found to selectively migrate from peripheral blood into decidua during pregnancy[9]. These cells have a dampening effect on the immune response, promoting tolerance of the semi-allogeneic fetus by secretion of cytokines, including TGFb and IL-10[10]. That they play a key role in promoting tolerance is demonstrated by a relative increase in their number in cases of fetal-maternal HLA-C mismatch[11]. Additionally, their numbers are decreased at the maternal-fetal interface in pregnancies complicated by severe early-onset preeclampsia, a disease characterized by abnormal EVT differentiation and incomplete physiologic conversion of maternal arterioles[10].

Chorionic Villi: Differentiation of Villous Trophoblast and Development of the Fetal Villous Tree

Chorionic villi are the functional units of the placenta. Villous formation begins with invagination of the primitive CTB layer around the blastocyst between 3 and 4 weeks of gestational age. Shortly thereafter, extraembryonic mesoderm (ExM), derived from the ICM, extends into the primitive villi, forming secondary villi (see Figure 1.1b). Between 5 and 6 weeks of gestational age, capillaries form within the villous core from the same ExM, thereby transforming these structure into tertiary villi (Figure 1.4). It is important to note that formation of fetal vessels within chorionic villi begins independently of vascularization within embryonic structures, including the umbilical cord, or cardiac development. Thus even anembryonic gestations can harbor primitive vessels within chorionic villi, though other signs of embryogenesis (such as infiltration of these spaces with nucleated red blood cells) will be absent.

First trimester villi consist of abundant mesenchyme surrounded by two continuous layers of trophoblast, the inner proliferative CTB layer, and the outer syncytiotrophoblast (Figure 1.4). Despite the name, the latter is considered distinct from the primitive syncytium, the layer of multinucleated cells which surround the early embryo and are responsible for initial implantation events. The primitive syncytium is more likely to be similar to implantation site EVT; in fact, some implantation site "giant cells" (see Figure 1.3b) may be remnants of the primitive syncytium. However, syncytiotrophoblast-proper arise by fusion of underlying CTB, a process that is mediated by the human endogenous retroviral gene products syncytins 1 and 2 (ERVW-1 and ERVFRD-1, respectively). Throughout gestation, CTB continue to proliferate, and subsequently fuse with and contribute to the overlying syncytiotrophoblast layer. However, since growth of the underlying stroma outpaces that of the trophoblast, over time, the trophoblast layer becomes thinner overall, and the CTB layer discontinuous (Figure 1.4)[12]. In the meantime, the nuclei of syncytiotrophoblast also undergo a maturation process, transitioning from an open, transcriptionally

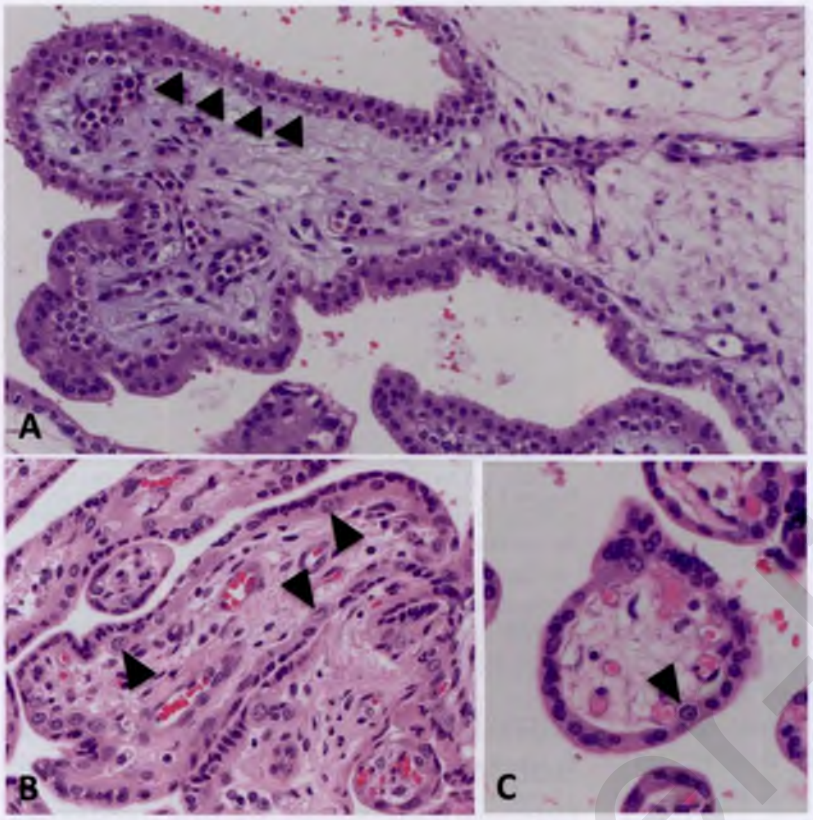

Figure 1.4 Chorionic villi across gestation. (a) Early tertiary villi, with a continuous layer of cytotrophoblast (arrowheads), which become discontinuous in the second trimester (b) with only occasional ones noted at term (c).

active euchromatin seen in nuclei of syncytial "sprouts," common in the first half of pregnancy, to the more condensed chromatin seen in nuclei of true syncytial "knots," aggregates which show evidence of oxidative damage and are common in post-term placentae[13]. Syncytiotrophoblast fragments are shed into maternal circulation as part of normal turnover of this tissue, a process that appears to be accelerated in some placental pathologies, including preeclampsia[14].

Following villous vascularization and formation of primitive tertiary villi, these structures undergo branching morphogenesis, a process by which chorionic villi develop from a group of relatively uniform structures, to ones where larger stem villi branch into intermediate and then into terminal villi, the primary sites of gas and nutrient exchange[4]. Branching morphogenesis is a complex process that requires close interaction and coordination between trophoblast and ExM-derived mesenchyme and fetal vasculature. In trophoblast, this process is mediated by induction of glial cells missing-1 (GCM1), a transcription factor previously identified as the "master" switch for development of the labyrinth, the equivalent of chorionic villi in mice[15]. In the human placenta, GCM1 in expressed in a subset of CTB and coordinates cell-cell fusion and syncytiotrophoblast formation, as well as branching morphogenesis[16]. Abnormalities in villous branching take many forms: they range from a decrease in properly formed terminal villi and thus gas and nutrient exchange interface in severe forms of preeclampsia and FGR, to the uncoupling of vasculogenesis and villous branching, resulting in excessive vessel formation in diabetic placentas.

Fetal Membranes

Initially after implantation, villous formation occurs concentrically in the CTB shell around the embryo (see Figure 1.1). However, beginning at 9 to 11 weeks gestation, villi furthest from the umbilical stalk begin to regress, forming the chorion laevae. At the same time, the free amniotic sac fuses with the chorionic mesenchyme. Later, between 18 and 20 weeks of gestation, as the gestational sac expands, these structures fuse with the endometrium opposite from the

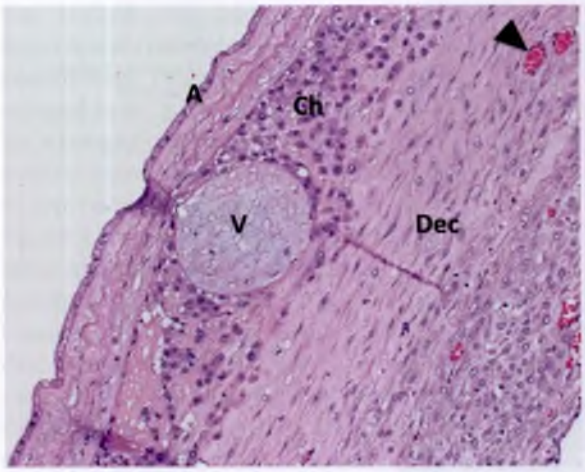

Figure 1.5 Fetal membranes at term, consisting of amnion (A), chorion (Ch), and decidua (Dec). The chorion can contain degenerated villi (V). Arrowhead points to a maternal vessel.

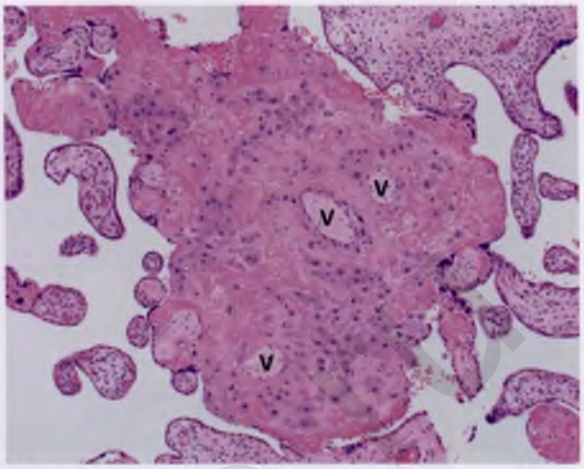

Figure 1.6 Intraplacental trophoblastic island, containing villus remnants (V), surrounded by perivillous fibrin, infiltrated by mature EVT with abundant amphophilic cytoplasm.

implantation site, leading to the placenta and the gestational sac occupying the entire uterine cavity[4]. Subsequently, at term, fetal membranes are seen to consist of a layer of amnion with a variable amount of underlying amniotic mesenchyme, chorionic trophoblast often containing villus "ghosts," and underlying decidua capsularis (Figure 1.5). Trophoblast of the chorion laevae (also called chorionic or membranous trophoblast) are considered extravillous trophoblast (EVT), insomuch as they are outgrowths of villi into surrounding matrix, similar to the process that occurs in anchoring villi at the implantation site. The decidua capsularis is often the most enriched source of maternal vessels; although not proven to be representative of maternal vessels in the decidua basalis (underlying the placental disc), vessels in this location are often used to evaluate for presence of lesions associated with hypertensive diseases of pregnancy (decidual arteriopathy and related lesions).

Intraplacental Trophoblast Islands

Another location where EVT arise from villus remnants is in intraplacental trophoblast islands within the placental disc (Figure 1.6). In this location, perivillous deposition of fibrin-type fibrinoid is part of the normal developmental process, which leads to degeneration of the syncytiotrophoblast, exposing the underlying CTB layer to the extracellular matrix. This leads to an induction of EVT differentiation, similar tooa the process in the fetal membranes and at the implantation site.

Extravillous Trophoblast: Terminology and Subtypes

Extravillous trophoblasts are referred to as intermediate trophoblast in a substantial portion of the placenta literature, probably because, when initially described, their morphology appeared to be "intermediate" between cytotrophoblast and syncytiotrophoblast. However, given our current knowledge of their biology – specifically, that they are a distinct lineage from villous syncytiotrophoblast – it is more accurate to refer to them as extravillous trophoblast (EVT).

EVT exist in several locations within the placenta: at the implantation site in the early gestation placenta and basal plate, in fetal membranes, and in intraplacental trophoblast islands. In all these locations, their differentiation is characterized by a transition from proliferative cytotrophoblast to a fully mature EVT. The more immature, "transitional" EVT is characterized by a vacuolated cytoplasm, and retention of p63 and Ki67, while "mature" EVT often has abundant eosinophilic-to-amphophilic cytoplasm, has fully lost expression of p63 and Ki67, and expresses HLA-G and MelCAM, among other markers[3]. In the basal plate, basal plate-type immature (transitional) EVT are located in the vicinity of the anchoring villi and mature as they infiltrate the underlying decidua. In the fetal membranes, membranous-type immature

(transitional) EVT are located in the layer of chorion closest to the amniotic mesenchyme, and they mature as they move closer to the decidua. In the intraplacental trophoblast islands, intraplacental type-immature (transitional) EVT are seen adjacent to villus remnants, located toward the center of the islands, with more mature EVT, seen toward the island periphery.

Knowledge Gaps

Large gaps remain in our knowledge of human placental development, including trophoblast differentiation. Both villous and extravillous trophoblast are likely to be much more heterogeneous than currently defined. Evaluation of this heterogeneity is required for identification of additional markers of trophoblast subtypes, which could then lead to a better characterization of differentiation defects in any given placental pathology. Similarly, better in vitro models of human trophoblasts, in co-culture with other cell types, and in 3D, are required to understand the placenta both during normal development and disease. Finally, little is known about development of this organ across gestation; therefore, establishment of noninvasive methods of evaluation, including imaging, with subsequent correlation with clinical and pathologic data, are needed to enhance our knowledge of this vital organ.

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Chapter 2

Early Pregnancy Loss with Normal Karyotype

Raymond W. Redline

Early pregnancy loss (EPL) is defined as premature delivery or nonviable status of an intrauterine pregnancy at 13 weeks gestation or less. Contemporary authors have emphasized that later pregnancy losses (14–20 weeks) have more in common with premature births, which are discussed in Chapter 31 and elsewhere in this book[1]. EPLs are clinically divided into two subgroups, embryonic (less than 10 weeks) and fetal (after 10 weeks)[2]. However, gestational age does not always correlate with developmental age, so it is useful, whenever possible, for pathology reports to begin by describing specimens in terms of their apparent stage of development. The following guidelines may be helpful[3]:

(1) An early first trimester chorionic sac (<8 weeks) has a thin chorion with scant, poorly branched, and incompletely vascularized villi; both chorion and villi have an edematous stroma without significant collagenization (Figure 2.1).
(2) A mid-first trimester chorionic sac (8–10 weeks) often has a detached amnion, early collagenization of chorion and proximal villi, and an intermediate volume of relatively homogeneous distal villi with clearly demarcated villous capillaries (Figure 2.2).
(3) A late-first trimester chorionic sac (>10 weeks) is characterized by fusion of the amnion and chorion, well-collagenized chorion and stem villi, thick-walled fetal vessels, and numerous villi with increasing demarcation between proximal and distal branches (Figure 2.3).

A useful theoretic framework for considering EPLs is to separate them into three categories:

(1) Inevitable loss of an intrinsically abnormal gestation
(2) Failure to maintain an otherwise normal gestation due to underlying maternal physiologic or structural problems
(3) Pathologic elimination of a normal gestation due to an active maternal disease process.

An EPL with a normal karyotype is significantly more likely to present as an early or late first trimester

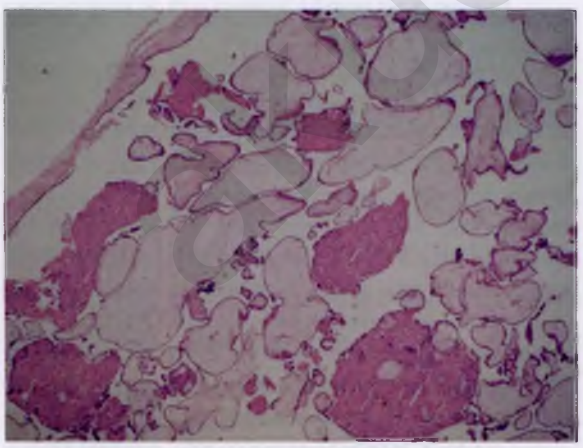

Figure 2.1 Early first trimester (6–8 weeks) chorionic sac with uniformly hydropic avascular villi; thin, poorly collagenized chorion; and no evidence of amnion, yolk sac, umbilical cord, or fetal/embryonic tissues (consistent with anembryonic pregnancy).

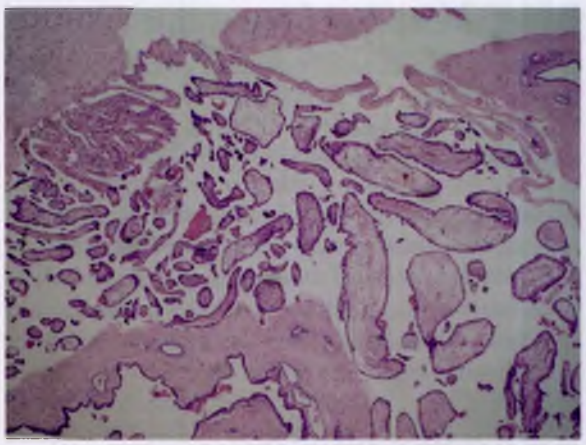

Figure 2.2 Mid-first trimester chorionic sac (8–10 weeks) with poorly vascularized, partially hyalinized, and hydropic villi, and partially collagenized chorion. Vascular involution and areas of edema and fibrosis reflect retention in utero following loss of viability. Note detached amnion epithelium (upper left).

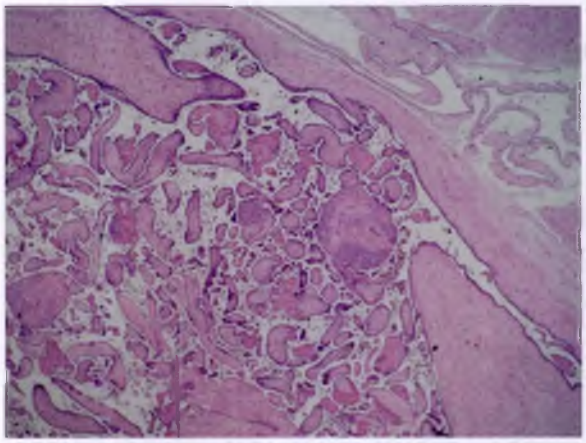

Figure 2.3 Late-first trimester chorionic sac (10–12 weeks) with uniformly fibrotic (hyalinized) avascular villi and a well-collagenized chorion with fused amnion (upper right). Vascular involution and areas of edema and fibrosis reflect in utero retention following loss of viability.

chorionic sac than an EPL with an abnormal karyotype[3]. Over 50 percent of EPLs have an abnormal karyotype compared with approximately 5 percent of elective early pregnancy terminations[4,5]. This chapter will focus on EPLs with a normal karyotype (Categories 2–3 and some cases in Category 1). Chapter 3 will address conceptions with an abnormal karyotype (the majority of Category 1). The topic of recurrent early pregnancy loss is further discussed in Chapter 35.

Developmentally Abnormal EPL with a Normal Karyotype (Anembryonic Pregnancy, "Blighted Ovum," Stunted/Nodular Embryo, Dysmorphic Villi)

Definition: Spontaneous passage or evacuation due to vaginal bleeding or intrauterine fetal death of an intrauterine pregnancy of <13 weeks with developmental abnormalities and a normal karyotype.

Clinical Context: A distinct subgroup of cytogenetically normal miscarriages have clear developmental abnormalities. Most of these present as missed abortions/fetal deaths by ultrasound, but some are passed spontaneously. Identification of these abnormalities in a nonkaryotyped first miscarriage is thought to be reassuring, suggesting a cytogenetic abnormality (see Chapter 3). However, these same findings in a second or, especially a third, miscarriage should prompt further investigation, starting with karyotype with more detailed clinical and molecular cytogenetic studies to be considered if the karyotype is normal.

Proposed Pathogenesis: Developmental abnormalities in the setting of a normal karyotype suggest the following possibilities:

(1) maternal contamination of the karyotyped specimen (false negative 46,XX)
(2) stochastic errors in embryonic development, possibly promoted by teratogens, nutritional factors, or an abnormal pregnancy environment
(3) genetic or epigenetic abnormalities undetectable by routine karyotype.

The contribution of genomic abnormalities not detectable by routine karyotype (mutations, insertions, deletions, copy number variations, uniparental disomy) is currently unclear, but small studies using comparative genetic hybridization and other molecular techniques suggest that they may explain up to 10–20 percent of abnormal EPL with a normal routine karyotype[6,7]. Other underlying abnormalities including undetected confined placental mosaicism, abnormal DNA methylation, and skewed inactivation of the X chromosome could explain additional cases but are difficult to detect and lack specific diagnostic criteria[8].

Gross Features: Lack of fetal/embryonic tissue, umbilical cord, yolk sac, and amnion at gross examination suggest an abnormality of early embryogenesis. Identification of an embryo that is abnormally small and malformed and lacks well-documented developmental milestones (stunted/nodular) provides additional support. While such abnormalities are seen in most chromosomally abnormal miscarriages with an identifiable embryo (90 percent of cases), they are also surprisingly common in specimens with a normal karyotype (74 percent of cases)[6].

Microscopic Features: An EPL following the clinical/radiologic diagnosis of anembryonic pregnancy often shows an early first trimester chorionic sac with uniformly hydropic, avascular villi and no evidence of amnion, yolk sac, umbilical cord, or fetal/embryonic tissue (Figure 2.1)[9]. In a population-based pathology-genetic correlation study, this phenotype was seen in 18 percent of miscarriages with an abnormal karyotype, compared to 9 percent having a normal karyotype[3]. Other dysmorphic features occasionally seen in the villi of cytogenetically normal miscarriages include irregular villous contour, trophoblast inclusions, enlarged villous stromal cell nuclei, abnormal villous vascular patterning, and nonspecific villous trophoblast hyperplasia (discussed and illustrated in Chapters 3 and 9). Since

only 2 percent of miscarriages with a normal karyotype in one study had two or more dysmorphic features, it could be argued that this finding should prompt consideration of genetic or epigenetic abnormalities not detectable by routine cytogenetic studies[3].

Ancillary Diagnostic Testing: Comparative genomic hybridization, SNP microarray testing, and analysis of maternal cell free fetal DNA may be useful in the further workup of selected cases. Complete genomic or exomic sequencing, karyotyping of tissue from multiple placental sites, and methylation profiling remain primarily research techniques. Immunohistochemistry for p57 and FISH for triploidy is sometimes required if gestational trophoblastic disease is in the differential diagnosis (see Chapter 4).

Prognostic Implications: Miscarriages occur in approximately 5 percent of first pregnancies and pregnancies following a normal delivery, roughly the same as the prevalence of abnormal karyotype in elective pregnancy terminations[10]. Incidence of miscarriage following a prior unsuccessful pregnancy on the other hand is 24 percent. These figures suggest that there may be recurring environmental, genetic, or epigenetic risk factors requiring further evaluation in cases that are normal by routine cytogenetic testing.

Knowledge Gaps: Aside from the 10–15 percent of cases with subkaryotypic genomic abnormalities, we have little insight into causation for this group. Among cases with genomic alterations, variants of unknown significance are difficult to evaluate. A cost-effective way to further evaluate morphologically abnormal miscarriages with a normal karyotype is needed.

Developmentally Normal EPL with a Normal Karyotype (Normal Embryo/Fetus; Early Vascular Karyorrhexis; Degenerative Changes including Hydropic, Hyalinized, Incompletely Vascularized, Or Avascular Villi; Recent Intervillous Hemorrhage; Hemorrhagic/Necrotic Gestational Endometrium)

Definition: Spontaneous passage or evacuation due to vaginal bleeding or intrauterine fetal death of a cytogenetically normal intrauterine pregnancy at <13 weeks lacking recognizable developmental abnormalities or histologic evidence of an active maternal disease process within the gestational tissues.

Clinical Context: The majority of apparently normal EPLs present clinically with vaginal bleeding and/or passage of tissue (spontaneous miscarriage/abortion, threatened, incomplete, or complete miscarriage/abortion). Some come to attention following ultrasound showing fetal death (missed abortion). Developmentally and karyotypically normal EPL have been associated with risk factors including early or late maternal age, obesity, smoking, maternal medical disorders including diabetes and hypothyroidism, in vitro fertilization, and a history of previous pregnancy complications including preeclampsia, fetal growth restriction, stillbirth, abruption, and spontaneous preterm birth[10,11].

Proposed Pathogenesis: Mechanisms implicated in failure to support an apparently normal early gestation can be grouped by category: structural (e.g. uterine anomalies), inadequate implantation (e.g. defective remodeling of decidual arterioles), hormonal (e.g. inadequate decidualization or poor luteal function), vascular (e.g. thrombophilia, hemorrhagic diatheses, hyperlipidemia, metabolic syndrome), teratogenic (e.g. illicit drug use or smoking), and nutritional (e.g. protein-calorie malnutrition or folate deficiency)[10,12–15]. The contribution of unrecognized genetic abnormalities is unknown.

Gross Features: Spontaneous EPL is often accompanied by a large volume of necrotic gestational endometrium and/or blood clot. Occasionally a well-formed "decidual cast" conforming to the outline of the endometrial cavity may be passed intact with the specimen. While these tissues may contain extravillous trophoblast confirming intrauterine pregnancy, optimal evaluation necessitates sampling of the chorionic sac. This sac can usually be identified by looking for a three-dimensional structure surrounded by numerous pale villous projections and attached membranous tissue. Embryonic/fetal tissue is less commonly seen.

Microscopic Features: Spontaneous EPL passed close to the time of fetal death generally show well-vascularized villi with early karyorhexis of fetal vascular endothelial cells and nucleated red blood cells (Figure 2.4). Secondary hydropic change, fibrosis, and involution of fetal vessels (poorly vascularized,

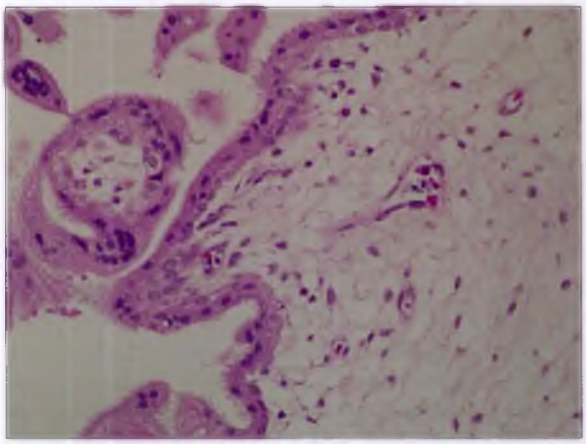

Figure 2.4 Early involutional changes in a spontaneously passed EPL: fetal endothelial cells and nucleated red blood cells with focal histologic karyorrhexis.

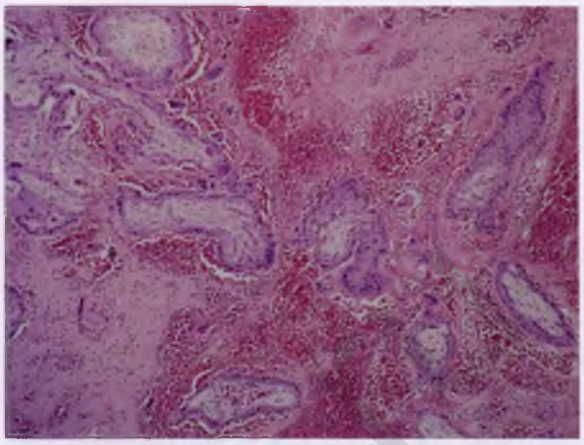

Figure 2.5 Abundant fresh intervillous hemorrhage, possibly reflecting failure of extravillous trophoblast to appropriately occlude decidual arterioles during early pregnancy.

partially hyalinized and hydropic villi) develop if the gestational sac is retained in utero for a prolonged period following fetal death (Figures 2.2 and 2.3). The intervillous space sometimes contains a large amount of fresh intervillous hemorrhage, possibly reflecting failure of extravillous trophoblast to appropriately occlude the decidual arterioles in early pregnancy (Figure 2.5). Excessive perivillous fibrin or chronic inflammation should prompt consideration of one of the active maternal disease processes discussed below. Gestational endometrium is usually necrotic, reflecting uteroplacental separation, with varying amounts of hemorrhage and nonspecific acute inflammation. Marked acute or chronic inflammation should prompt consideration of infection (see Chapter 12). Plasma cells or chronic vasculitis may indicate an immune mechanism (see below).

Ancillary Diagnostic Testing: Comparative genomic hybridization, SNP microarray testing, and analysis of maternal cell free fetal DNA may be useful in the further workup of selected cases.

Prognostic Implications: A developmentally normal EPL with normal karyotype is less reassuring for future pregnancy outcomes than the finding of developmental abnormalities. Recurrence risk depends on whether there are persistent underlying risk factors. In practical terms, the best indicator of future risk is probably the outcome of the next pregnancy which usually distinguishes random stochastic errors from underlying pathogenic processes.

Knowledge Gaps: What distinguishes patients with recurrent apparently normal EPL from patients with similar risk factors and normal pregnancy outcomes remains unclear.

Active Maternal Disease Processes, Immune, Vascular, and Infectious (Massive Perivillous Fibrin Deposition, Chronic Histiocytic Intervillositis, Lymphoplasmacytic Deciduitis, Chronic Villitis, Decidual Vasculitis)

Definition: Spontaneous passage or evacuation due to vaginal bleeding or intrauterine fetal death of an intrauterine pregnancy at <13 weeks showing histologic evidence of an active maternal disease process

Clinical Context: Active maternal disease processes can affect EPL with or without a normal karyotype. However, histologic evidence of these processes has a high predictive value for normal karyotype (see below). They are most common in the mid-late first trimester. Congenital infections (TORCH-type) represent a distinct subgroup of cases and are discussed in Chapter 12. Noninfectious active maternal disease processes in EPL are more common in mothers with autoimmune disease, inherited thrombophilia, and primary antiphospholipid antibody syndrome[3,16]. They may also reflect immune mechanisms related to a maternal alloimmune response action to paternal antigens in the fetus[17].

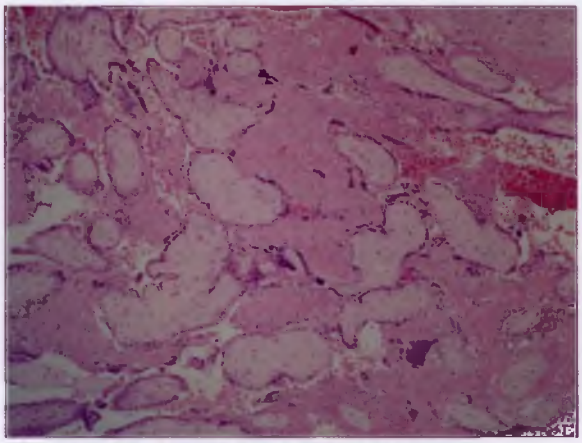

Figure 2.6 Massive perivillous fibrin deposition (maternal floor infarction): intervillous space is effaced by a matrix-type fibrinoid that completely surrounds the distal villi.

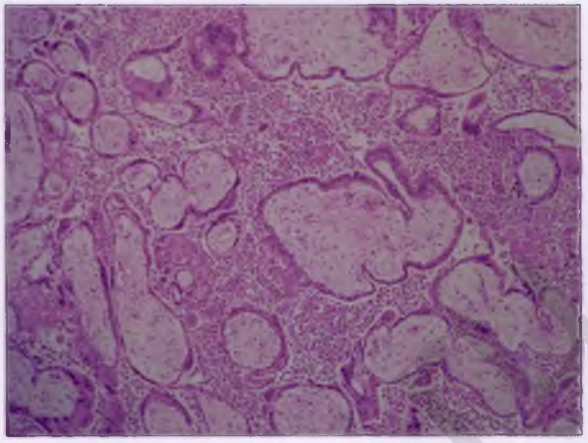

Figure 2.7 Chronic histiocytic intervillositis (massive chronic intervillositis): intervillous space is diffusely infiltrated by a monomorphic infiltrate of maternal monocyte-macrophages.

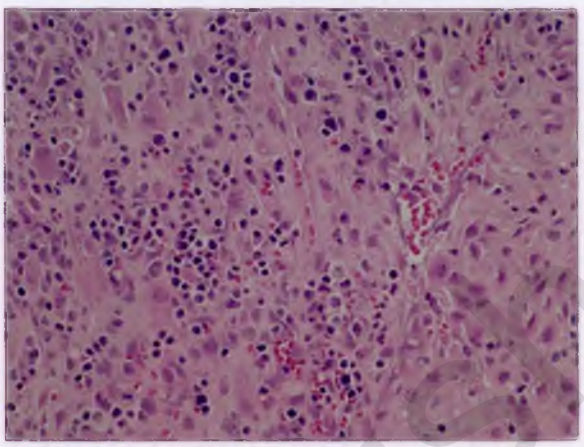

Figure 2.8 Lymphoplasmacytic deciduitis: numerous endometrial plasma cells indicate inappropriate local antigen stimulation.

Accepted management options include low dose heparin for the antiphospholipid syndrome and corticosteroids for maternal autoimmune diseases[2]. Other therapies sometimes employed include progesterone supplementation, low-dose aspirin, and use of immunosuppressive agents in cases of chronic histiocytic intervillositis (see Chapter 15)[18].

Proposed Pathogenesis: Successful pregnancy requires maintenance of an adequate maternal blood supply, local immunosuppression to protect the fetus from rejection, and reciprocal interactions between maternal and fetal cells to promote normal growth and development. Coagulopathy, autoimmune vasculitis, antigen-specific immune responses, and stimulation of innate immunity could all potentially interfere with these processes, leading to EPL.

Gross Features: Active maternal disease processes can be seen at any gestational age and may present with either spontaneous passage or retention of a nonviable gestational sac. They are most common in mid to late first trimester gestations and commonly have accompanying amnion, yolk sac, umbilical cord and/or embryonic/fetal fragments.

Microscopic Features: Histologic findings suggesting a noninfectious active maternal disease process include massive perivillous fibrin deposition, chronic histiocytic intervillositis, lymphoplasmacytic deciduitis, chronic villitis, and decidual vasculitis[3]. Massive perivillous fibrin deposition can occur at any gestational age and is covered in detail in Chapter 17. It is characterized by effacement of the intervillous space by a matrix-type fibrinoid that completely surrounds and envelops the villous tree and is usually accompanied by clusters of intraplacental extravillous trophoblast, also known as "X-cells" (Figure 2.6). Chronic histiocytic intervillositis is most common in EPL, but can present later in pregnancy. It is discussed in detail in Chapter 15 and is characterized by diffuse infiltration of the intervillous space by a monomorphic infiltrate of CD68-positive maternal monocyte-macrophages, sometimes accompanied by variable amounts of intervillous fibrin (Figure 2.7). Endometrial plasma cells always indicate inappropriate local antigen stimulation, whether in pregnant (lymphoplasmacytic deciduitis) (Figure 2.8) or

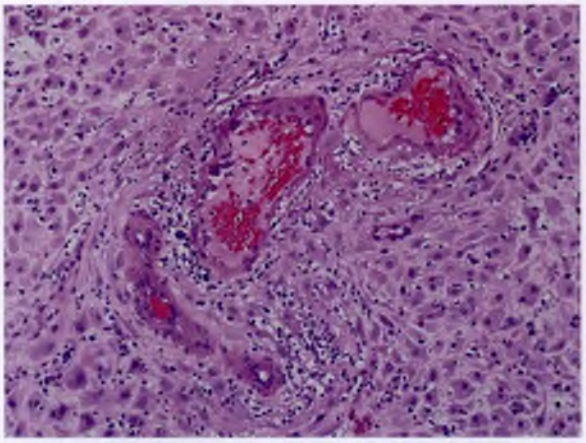

Figure 2.9 Decidual vasculitis: small arterioles with a chronic perivascular infiltrate of mononuclear and plasma cells focally infiltrating and disrupting the vascular wall.

nonpregnant endometria (chronic endometritis). Lymphoplasmacytic deciduitis is further discussed in Chapter 14. When accompanied by chronic villitis (villitis of unknown etiology [VUE]), which is rare in EPL, it is considered to be a form of host versus graft reaction. Decidual vasculitis is a less well-characterized entity sometimes seen in patients with recurrent miscarriage and is often associated with one or more maternal serum autoantibodies (e.g. low titer antinuclear antigen). It is defined by mononuclear cell infiltration of the muscularis and/or intima of small decidual arteries or arterioles with or without accompanying neutophils or plasma cells[19,20]. It can also be also associated with mural edema or muscular hypertrophy (Figure 2.9). These findings are subtle and should be diagnosed with caution, especially in the presence of obscuring ischemic necrosis or acute inflammation.

Ancillary Diagnostic Testing: Specific immunohistochemical stains may be employed if infection is in the differential diagnosis (e.g. CMV, toxoplasmosis, parvovirus).

Prognostic Implications: In a population-based study, histologic evidence of an active maternal disease process was strongly associated with normal karyotype[3]. Chronic histiocytic intervillositis and massive perivillous fibrin deposition, in particular, had a positive predictive value for normal karyotype that exceeded 85 percent. More significantly, active maternal disease was dramatically increased in cases of recurrent EPL with a normal karyotype (31 percent), compared to recurrent EPL with an abnormal karyotype (11 percent) and nonrecurrent EPL (12 percent). These findings may be helpful for clinicians in deciding whether to undertake a comprehensive diagnostic workup and/or initiate therapy.

Knowledge Gaps: The cellular mechanisms initiating and promoting local active maternal disease processes are poorly understood. Underlying maternal genetic risk factors, if any, are unknown.

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Chapter 3

Early Pregnancy Loss with Abnormal Karyotype

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Early pregnancy loss (EPL) is defined as premature delivery or nonviable status of an intrauterine pregnancy at 13 weeks gestation or less.[1] As discussed in the previous chapter, a useful framework is to separate these losses into three categories: (1) natural loss of an intrinsically abnormal gestation, (2) failure to maintain an otherwise normal gestation due to maternal structural or hormonal issues, and (3) pathologic elimination of a normal gestation due to an active maternal disease process. This chapter will focus on EPLs with an abnormal karyotype by routine cytogenetic analysis (aneusomy and polyploidies). These constitute the majority of cases in Category 1.[2,3] Over 50 percent of spontaneous EPLs have an abnormal karyotype compared with approximately 5 percent of elective terminations. The percentage with karyotypic abnormalities is highest prior to 6 weeks (70 percent), intermediate at 6–10 weeks (45 percent), and declines after 10 weeks (less than 20 percent). An abnormal karyotype can manifest clinically as inappropriately low levels of human chorionic gonadotropin (hCG), failure to develop a yolk sac or fetal pole, reduced diameter of the chorionic sac, fetal growth restriction, and/or an abnormal fetal heart rate, but all of these findings are nonspecific. Certain pathologic findings (dysmorphic villi) are highly specific for abnormal karyotype, but are only seen in in a minority of cases, as discussed below.

Abnormal Karyotypes without Dysmorphic Villi (Anembryonic Pregnancy, "Blighted Ovum," Nodular / Stunted Embryos, Involutional Changes: Hydropic / Hyalinized / Poorly Vascularized / Avascular Villi)

Definition: Genetically abnormal (aneusomic/polyploid) conception without specific histopathological abnormalities

Clinical Context: Most EPLs with abnormal karyotypes (83 percent) lack dysmorphic villi.[4] The majority of these specimens are identified by ultrasound as nonviable pregnancies ("missed abortions") and evacuated by curettage, but some pass spontaneously. They can present at any stage of development, but two phenotypes are most common; early anembryonic pregnancies (<8weeks) with uniformly hydropic avascular villi and later chorionic sacs (8 weeks or greater) with secondary involutional changes (poorly vascularized, partially hyalinized, and hydropic villi).[5]

Proposed Pathogenesis: Most aneusomies are the consequence of nondisjunction of chromosomes during meiosis.[2] A minority involve inherited unbalanced translocations or other marker chromosomes inherited from a parental carrier. Triploidy is caused by either dispermy or fertilization of a diploid egg.[6] Higher order polyploidies usually arise via endoduplication of chromosomes without cytokinesis[7]. Lack of fetal development and deficient villous vascularization due to abnormal gene expression are believed to result in arrested placental development and loss of viability.

Gross Features: Gross findings depend on clinical presentation. Spontaneously passed specimens often have a relatively intact chorionic sac, usually without a recognizable fetus, and large amounts of hemorrhagic gestational endometrium and clotted blood. Occasionally an intact decidual cast with or without an attached chorionic sac is seen. Curettage specimens are more likely to show fragments of decidua (shiny surface and rough filamentous underside) and a disrupted mid to late first trimester chorionic sac, best recognized by the presence of filmy membranous tissue. The embryo/fetus, if present, is often dysmorphic (nodular/stunted) or small for gestational age. In rare cases, discrete congenital malformations can be identified.

Microscopic Features: Anembryonic pregnancies generally show features indicative of an early first trimester chorionic sac (thin chorion with scant poorly branched and incompletely vascularized villi, both showing a similar edematous stroma without collagen). Distal villi lack any fetal vessels, resulting in hydropic degeneration due to continuing trophoblastic function, transporting fluid and electrolytes into the stroma from the maternal circulation (see Figure 2.1). In cases of prolonged retention, uniformly hydropic avascular villi convert to uniformly fibrotic/ hyalinized avascular villi. As discussed in the previous chapter, this "anembryonic" phenotype is observed in 18 percent of miscarriages with an abnormal karyotype compared with 9 percent having a normal karyotype[4]. However, the positive predictive value of this finding (70 percent) is not high enough to make it clinically useful. EPLs with an abnormal karyotype and more advanced fetoplacental development show features of a mid to late first trimester chorionic sac (collagenized chorion, distinction between proximal and distal villi, large fetal vessels, and accessory structures such as amnion, a yolk sac, an umbilical cord, or rarely a fetus (see Figures 2.2 and 2.3). Distal villi show a mixture of hydropic and fibrotic changes (hyalinization), with the latter becoming predominant at later gestational ages. Remnants of involuting fetal villous vessels are usually apparent. Gestational endometrium in cases without vaginal bleeding or passage of tissue is generally well preserved with only focal necrosis or hemorrhage.

Ancillary Diagnostic Testing: Further testing in addition to karyotype is not generally required.

Prognostic Implications: A sporadic EPL with an abnormal karyotype and no dysmorphic features is generally associated with a good prognosis for future pregnancies. An exception would be cases associated with parental translocation carrier status. Recurrent losses with abnormal karyotypes are poorly understood but may reflect genetic defects in meiosis or parental gonadal mosaicism.

Knowledge Gaps: While EPLs with an abnormal karyotype are common and generally nonrecurrent, the majority of women do not suffer such losses. Whether this is random chance or reflects underlying biologic factors is unknown.

Abnormal Karyotype with Dysmorphic Features (Atypical Villus Morphology, Irregular Villous Contour, Trophoblast Inclusions, Stromal Nuclear Karyomegaly, Nonspecific Trophoblast Hyperplasia, Abnormal Vascular Patterning, Villous Cisterns)

Definition: Genetically abnormal (aneusomic/polyploid) conceptions with specific histopathologic abnormalities grouped under the heading of dysmorphic villi or atypical villus morphology.

Clinical Context: The finding of dysmorphic villi by an experienced pathologist is highly specific for an abnormal karyotype in most studies.[4,8–13] In one population-based study the positive predictive value after finding two or more dysmorphic features (see below) was 90 percent[4]. However, less than a quarter of karyotypically abnormal specimens (17 percent) showed these findings, so the negative predictive value was low (48 percent). It follows that identification of dysmorphic villi in an unkaryotyped EPL is reassuring, suggesting a random meiotic error unlikely to recur in subsequent pregnancies. Specimens with dimorphic small and large villi, villous cisterns, trophoblast hyperplasia, and other dysmorphic features, are partial hydatidiform moles requiring specific clinical follow-up (see Chapter 4). Trophoblast hyperplasia alone is increased with some abnormal karyotypes (see below) and, when diffuse, should prompt consideration of at least a single follow-up hCG titer to exclude gestational trophoblastic disease (see Chapter 4).[14]

Proposed Pathogenesis: Abnormal gene dosage presumably causes specific developmental defects that lead to villous dysmorphogenesis.

Gross Features: EPLs with abnormal karyotype and dysmorphic villi share gross characteristics with those lacking dysmorphic villi. Cystic villi (greater than 2 mm in diameter) are commonly see with triploidy and tetraploidy.

Microscopic Features: Specific dysmorphic features include the following: *Irregular villous contour* characterized by scalloping and fjord-like invaginations affecting the entire distal villous tree.[15,16]

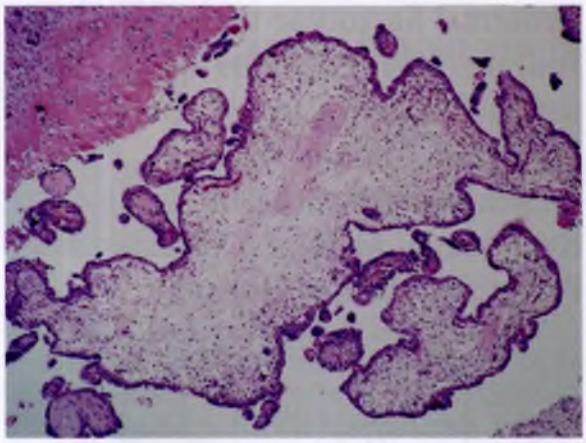

Figure 3.1 Irregular villous contour: scalloping and fjord-like invaginations affecting the entire distal villous tree.

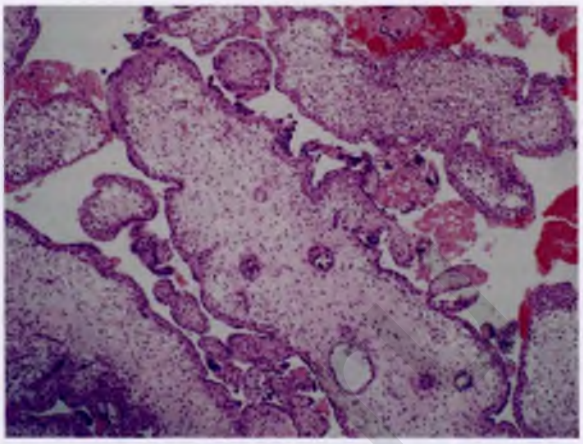

Figure 3.2 Trophoblast inclusions: epithelial cysts/nests of villous-type trophoblast within the villous stroma.

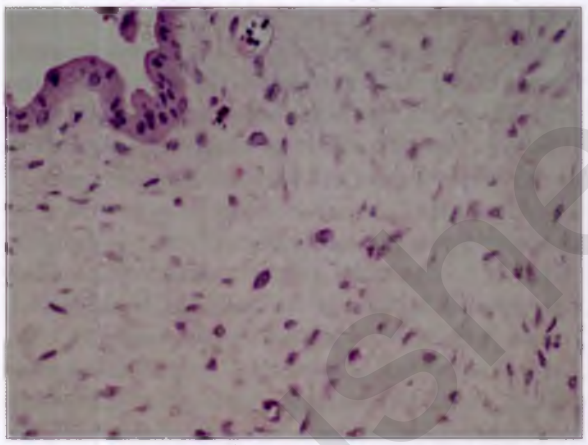

Figure 3.3 Villous stromal cells with nuclear karyomegaly: cells with two- to threefold enlargement of nuclear area compared with adjacent normal stromal cell nuclei.

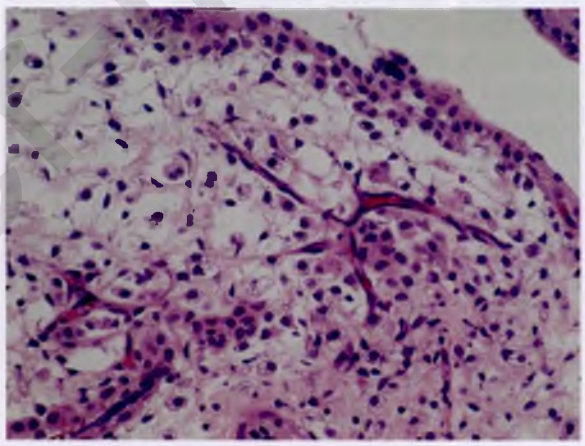

Figure 3.4 Abnormal vascular patterning: perpendicular, "maze-like" capillary branching.

The abnormal contour is best described as irregularly irregular, meaning that both large and small areas of scalloping are noted (Figure 3.1). *Trophoblast inclusions* may occasionally represent oblique sectioning of villi with an irregular contour, but most are true epithelial inclusions – possibly budding off from the villous trophoblast and dropping into the stroma due to an increased proliferative rate of the inner cytotrophoblast relative to the outer syncytiotrophoblast layer (Figure 3.2).[17] *Isolated villous stromal cells with nuclear karyomegaly* are most common with triploidy or higher order polyploidies (Figure 3.3).[18] They can be of either trophoblastic or histiocytic origin. *Abnormal vascular patterning* usually manifests as a maze-like ("chicken-wire") capillary network, but isolated irregularly branching villous capillaries, dilated venous sinusoids, and/or unusually large muscularized vessels within distal villi are other commonly seen abnormal patterns (Figures 3.4 and 9.15)[15,19]. *Villous* cisterns represent clearing of stromal cells

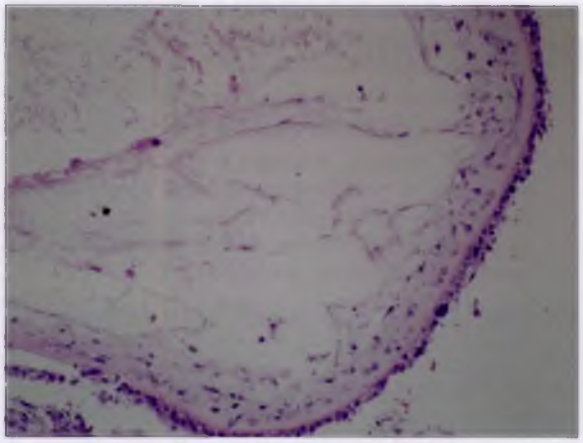

Figure 3.5 Villous cistern formation: accumulating edema fluid with loss of stromal cells in the central portion of a markedly hydropic villus leaving just a thin stromal mantle at the periphery.

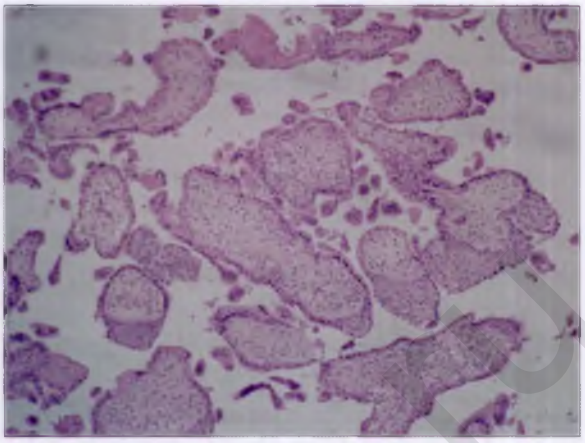

Figure 3.6 Nonspecific villous trophoblast hyperplasia (45,XO): syncytiotrophoblastic sprouts projecting into the intervillous space (apparently detached in some planes of section).

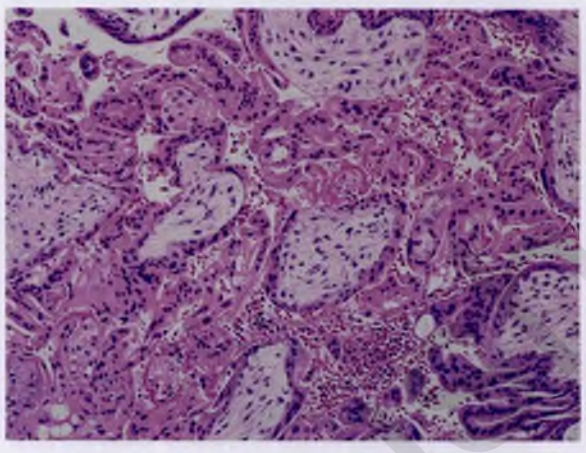

Figure 3.7 Nonspecific villous trophoblast hyperplasia (47XY,+7): abundant, markedly thickened syncytiotrophoblast extending into the intervillous space.

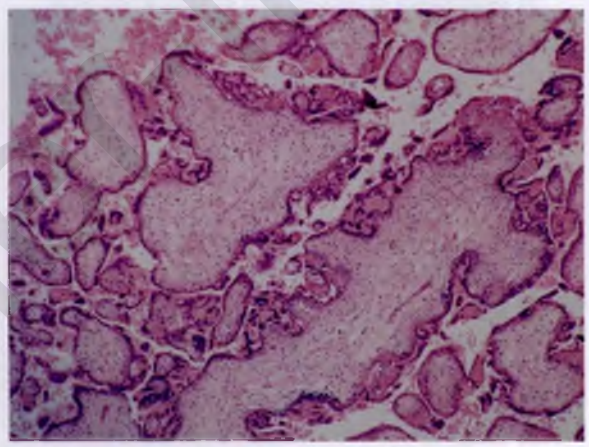

Figure 3.8 Nonspecific villous trophoblast hyperplasia (47XX,+16): complex papillary/microcystic trophoblastic proliferation covers most distal villi.

from the central portion of hydropic villi leading to a thin stromal mantle just below the villous trophoblast (Figure 3.5). Cisterns commonly develop when cystic villi exceed 2 mm in diameter[4,15]. Significant *villous trophoblast hyperplasia* may be seen with several specific chromosomal anomalies including trisomies 7, 15, and 22; monosomy X; and diandric triploidy[14]. Abnormal trophoblast sprouts (Figure 3.6), markedly thickened and occasionally vacuolated syncytiotrophoblast (Figure 3.7), and complex papillary and microcystic proliferations (Figure 3.8) are among the different patterns that can be seen.

Ancillary Diagnostic Testing: Further testing in addition to karyotype is not generally required.

Prognostic Implications: Dysmorphic villi have a high predictive value for abnormal karyotype when diagnosed by an experienced observer.

Knowledge Gaps: Dysmorphic villi are more frequent in certain specific trisomies. However, not all specimens with the same karyotype show the same atypical villus features[20]. Whether non-molar trophoblast hyperplasia ever progresses to trophoblastic malignancy is not known.

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Chapter 4

Gestational Trophoblastic Disease

Bradley J. Quade

The neoplastic trophoblastic lesions to be considered in this chapter are distinctive because they are products of conception. Consequently, they are genetically distinct from the host in which they reside. Their special nature is underscored by a commonly used synonym, gestational trophoblastic disease. Nearly all pregnancy-related tumors and tumorous proliferations resemble cells constituting the placenta in normal pregnancy. That such is the case is not surprising when one considers the biology of the placenta. As the placenta forms and grows to form the vital interface with the mother, its trophoblast invade the stroma and blood vessels of the endometrium and superficial myometrium. Trophoblast cells also may detach and circulate within the maternal blood. Dysregulation of these developmental processes form the basis of local invasion and distant metastasis observed in gestational trophoblastic neoplasia. The pathogenesis of gestational trophoblastic neoplasia stems mostly from genetic errors occurring during fertilization. The nosology of trophoblastic tumors, however, is organized based on our recognition of phenotypic similarities to trophoblast found in the various compartments of normal placentas, beginning with the presence or absence of chorionic villi.

Villous Trophoblastic Lineage

Partial Hydatidiform Moles

Definition: A partial hydatidiform mole is one of two forms of molar pregnancy in which there is a pathologic trophoblastic proliferation forming molar chorionic villi[1,2]. Although a partial mole shares some genetic and histological features with a complete mole, the potential for adverse clinical outcome is significantly lower. (The less experienced reader may find it helpful to read the section on complete hydatidiform moles first; see below).

Clinical Context: A partial mole is one form of gestational trophoblastic disease in which substantial embryonic development occurs. Although fetal cardiac activity may be observed, there is a high rate of intrauterine demise, usually by 8 to 9 weeks gestational age[3]. Consequently, a partial mole often presents as missed or incomplete abortion, usually with late first trimester bleeding and uterine size too small for the estimated gestational age[4]. The risk of a partial mole is about 1 to 3 per 1,000 live births[5,6].

Proposed Pathogenesis: Like complete hydatidiform moles, the fundamental pathobiological problem in partial moles is an imbalance in the genetic contributions from both parents[7]. Both forms of hydatidiform mole have excess paternal hereditary material. The key distinction in partial moles is the retention of at least one maternal haploid genome.

The most common form of partial mole is triploidy (i.e. having 69 chromosomes)[8,9]. This genetic situation can arise when an oocyte, which retains one haploid genome, is fertilized by either two separate sperm, each having one haploid genome, or a single diploid sperm. In either case, the product of conception has diandric triploidy. It is important to appreciate that triploidy alone is not sufficient to result in the partial molar phenotype. Digynic triploidy in fact results in a milder abnormalities such as irregular contours, dimorphism, minimal trophoblast hyperplasia, and sclerosis, but never hydropic degeneration or overall features suspicious for partial moles[9].

Alternate genetic mechanisms may also rarely lead to partial moles. In one unusual case, extra copies of chromosomes 3, 7, and 8 of paternal origin resulted in the histomorphology of a partial mole[10]. Incomplete androgenetic excess in tetraploid gestations (i.e. a genotype composed of three paternally and one maternally derived alleles (PPPM) with respect to parent of origin for any given locus) may also produce the partial molar phenotype[11]. That said, the majority of partial moles are triploid[12].

Gross Features: Relative to complete moles, partial hydatidiform moles have relatively subtle gross placental phenotypes. The extent of villous swelling is not

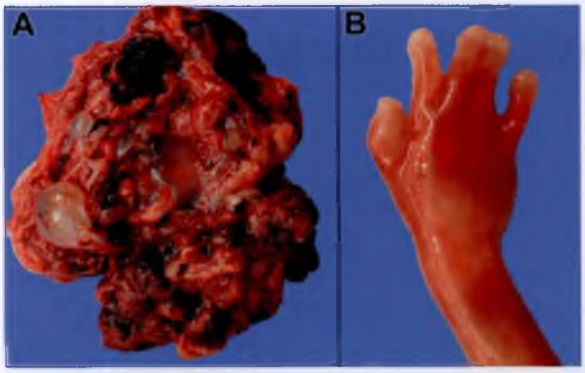

Figure 4.1 Partial hydatidiform mole may have macroscopically visible scattered cysts of various sizes intermixed with more normal appearing placental tissues (a) and fetal parts (b). Although many fetal abnormalities may occur, one of the most helpful, as well as most likely to be found, is syndactyly between the third and fourth digits.

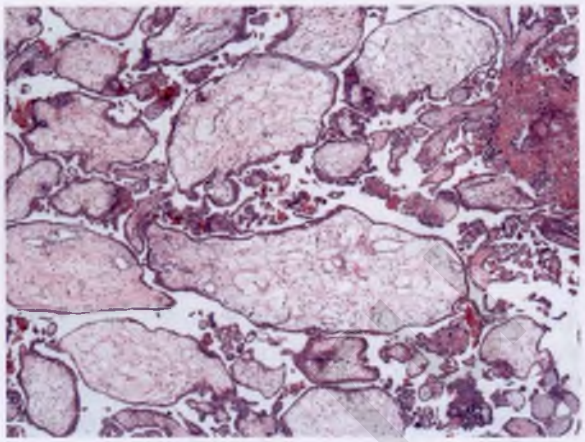

Figure 4.2 A partial hydatidiform mole consists of two distinct populations of villi, one with normal villi and the other with enlarged, scalloped villi. Note how the two populations are mixed together, which distinguishes them from hydropic degeneration.

as extreme, typically only a few millimeters in greatest dimension and affecting only a fraction of villi (Figure 4.1a). Recognizing such cystic villi admixed with grossly normal villi requires careful attention and is often missed.

An important distinction between partial and complete moles is the presence of fetal development. Evidence of degeneration is not uncommon, as first trimester loss is typical. Careful examination often reveals syndactyly in the hands and feet. Fusion of digits 3 and 4 in the hands is particularly characteristic, being identified in nearly 70 percent of triploid fetuses (Figure 4.1b)[13]. The spectrum of other findings includes facial and other limb anomalies, as well as microcephaly and neural tube defects[14].

Microscopic Features: Partial molar histology is classically described as having intermixed populations of chorionic villi differing in size and shape (Figure 4.2). One of the admixed populations appears relatively normal; however, villi in the other population are distinctly enlarged and have irregular, scalloped contours (Figure 4.3a). It is said that trophoblast hyperplasia is present in partial moles, but relative to the yardstick of complete moles, trophoblast hyperplasia is modest[9]. As the villus enlarges, the trophoblast hyperplasia manifests as a proliferation of the cytotrophoblast and syncytiotrophoblast layers that matches the size enlargement (Figure 4.3b). In some villi, the trophoblast proliferation may be slightly in excess, producing filiform or lacy extensions of trophoblast cytoplasm that appeared to form "free-floating" tags in tissue sections (Figure 4.3b). An important feature distinguishing the trophoblast in hydatidiform moles is the loss of polarity seen in well-regulated normal villi. The trophoblast proliferation may be slightly atypical relative to normal villi. True cavitation with clear fluid accumulating within the stromal core is present, but not as frequent as that seen in complete moles (Figure 4.3a). Other helpful features include observation of frequent well-formed blood vessels and nucleated fetal red blood cells, as well as occasional fragments of embryonic tissue. Up to 10 percent of partial moles also have an atypical implantation site (see "Exaggerated Implantation Site Reaction/Atypical Implantation Site," below)[15]. When considering the histological features of partial mole, it is helpful to know that no single parameter is sufficiently specific or sensitive, and one should require presence of multiple features before making the diagnosis[16].

Differential Diagnosis: The principal differential diagnosis for partial hydatidiform mole includes complete hydatidiform mole, hydropic abortus, aneusomy, and digynic triploid gestation. In general, the histological findings of partial mole, particularly trophoblast hyperplasia and cavitation, are less extreme than for complete mole. In addition, recognition of the two morphologically distinct but admixed populations of villi are a helpful indication favoring a partial mole. The notable exception to this approach is twin

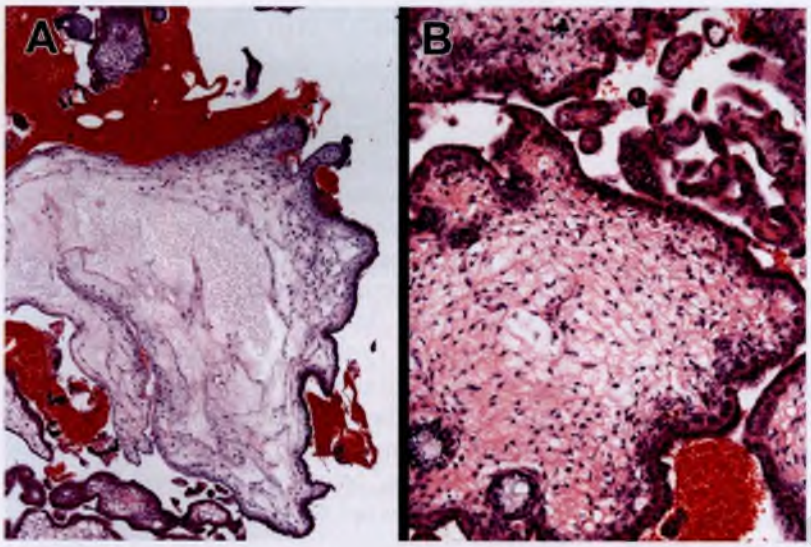

Figure 4.3 Partial hydatidiform moles have scattered cavitated villi (a) and convoluted or scalloped villi with deep invaginations and trophoblast hyperplasia manifested as a lack of trophoblast attenuation on their surface and exuberant trophoblast tags extending into the intervillous space (b).

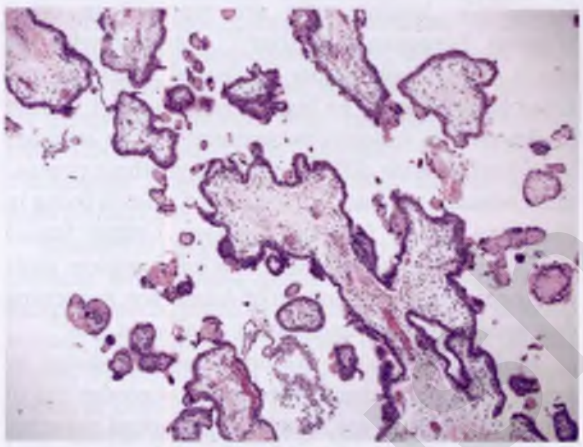

Figure 4.4 Aneusomy, usually trisomies, of various chromosomes may have dysmorphic villi with enlargement and scalloped shapes of such complexity that they may mimic partial molar villi. A first trimester placenta with trisomy 13, one of the more common etiologies, is illustrated.

gestation with one normal gestation and one complete molar gestation (see "Hydatidiform Mole in a Twin Gestation," below). In addition, a complete mole typically lacks evidence of fetal development. Distinction from hydropic abortus is facilitated by observing the uniformity of villous enlargement, sometimes in regional groups, rather than as intermixed populations of enlarged and non-enlarged villi. In addition, the swelling of the villi of hydropic abortus is not accompanied by trophoblast hyperplasia. The result of this decoupling of size and trophoblast proliferation is progressive attenuation of the trophoblasts in hydropic villi. The most challenging entity from which partial molar gestations must be distinguished are other aneusomies (Figure 4.4). Chromosomally abnormal or digynic triploid gestations often have villi with dysmorphic and enlarged villi. Such chromosomally abnormal villi, however, rarely cavitate.

Ancillary Diagnostic Testing: Histologic evaluation alone for the diagnosis of partial mole has a sensitivity of 88 percent and a specificity of 89 percent. Thus, diagnostic accuracy may benefit by incorporating additional tools into routine diagnostic workflow.

Techniques capable of detecting triploidy include flow cytometry, karyotyping, fluorescence, and chromogenic *in situ* hybridization, and genotyping by microsatellite or single nucleotide polymorphisms, but it must be understood that a diagnosis of triploidy is not equivalent to diagnosis of partial mole[17–25]. To distinguish diandry from digyny, rigorous evaluation must include parental genotyping and assessment of histologic features. While elaborate schema may be applied for research studies, especially for understanding rather rare and unusual genetic mechanisms, knowledge of triploidy without knowing parental origin may be helpful when evaluating cases in which histology is suggestive but not quite diagnostic of a partial mole (e.g. small specimens or ones without cavitated villi). In our practice, we are content to make the diagnosis of a partial mole for samples having *both* triploidy and dysmorphic villi.

In cost-conscious or resource-limited environments, it may be more practical to focus on using p57 immunohistochemistry, which excludes the diagnosis of complete mole and unusual variants such as androgenetic biparental mosaicism / chimerism (see Chapter 9) or molar co-twinning[26]. While the various modalities of ancillary testing may facilitate a more accurate diagnosis, its addition does not help determine the likelihood of persistent gestational trophoblastic disease in our experience.

Prognostic Implications: The implications of a diagnosis of partial mole have evolved with genetic investigation and the development of sophisticated ancillary testing. Well-documented cases of partial moles developing into choriocarcinoma are rare[27–29]. In the pre-p57 era of molar diagnostic classification, about 5–10 percent of patients with partial moles, particularly those of older age or a prior history of molar pregnancy, developed non-metastatic, persistent gestational trophoblastic disease[28,30,31]. That said, the risk of developing choriocarcinoma or other trophoblastic malignancies after a partial mole is probably less than 2 percent and may well be closer to the risk for normal pregnancies. Such prognostic discrepancies may reflect differences in diagnostic reproducibility occurring before and after incorporation of advances in the molecular genetic understanding of molar gestations into routine diagnostic regimens[32]. Furthermore, patients with partial moles developing persistent gestational trophoblastic diseases, usually defined by persistent beta human chorionic gonadotropin (β-hCG) abnormalities, achieve complete remission with either chemotherapy or second uterine evacuation, and histologic examination of second evacuation samples is more reminiscent of retained products of conception than malignant trophoblast disease. Current management for a partial mole by most clinicians includes weekly follow-up β-hCG determination until three consecutive normal tests are achieved, followed by a minimum of three consecutive normal monthly tests.

Knowledge Gaps: The precise level of risk for malignant outcome following partial mole and thus the duration and intensity of post-molar serum β-hCG monitoring remains a subject for debate.

Complete Hydatidiform Moles

Definition: Complete hydatidiform mole is the other principal form of molar pregnancy in which there is a pathologic proliferation of cytotrophoblast, syncytiotrophoblast, and villous mesenchyme that in aggregate forms molar chorionic villi. Complete hydatidiform mole is the product of an aberrant fertilization. As the gestational age increases, the molar villi uniformly grow to macroscopic size, forming grape-like cysts. This entity is so named to describe the "water drop" cysts (Greek "hydatisia") clustering together and forming a false conception (Latin "mole"). Non-villous implantation site atypia (see "Exaggerated Implantation Site Reaction/Atypical Implantation Site," below) is often noted. Embryonic development does not occur.

Clinical Context: Hydatidiform moles occur at a rate slightly less than 1 in 1,000 pregnancies in the United States[33,34]. Similar rates are reported in other Western European countries[35]. Interestingly, the rate is substantially higher in Central American and Asian populations. The highest rate (nearly 1 in 100) is observed in Indonesian women[33]. The etiologic basis for this wide difference between ethnic populations remains unclear, but a study of women living in the same region (the northeastern United States) found that the age-adjusted risk of complete mole was indeed higher in women of Asian race, suggesting that genetic background plays a significant role[5].

Molar pregnancy is not uniformly distributed by age[33,35–38]. Peripubertal females are at greater risk of complete moles as are females of advanced maternal age. Specifically, females older than 35 have a twofold increased risk, and females older than 40 have a five- to tenfold increased risk. Other implicated risk factors include low socioeconomic status, prior molar pregnancies, and nulliparity.

Clinical features at presentation depend on gestational age. After 12 weeks of gestation, the classical presentation of a complete hydatidiform mole includes painless vaginal bleeding, a uterus large for gestational ages, hyperemesis, preeclampsia prior to 20 weeks gestational age, hyperthyroidism, ovarian theca lutein cyst development, and an absence of fetal parts or heart tones. These clinical features reflect abnormal implantation, as well as the bulk and hormonal effects from the massive amounts of hyperplastic and hydropic chorionic villi. The "snowstorm" or "Swiss cheese" ultrasound

appearance of classical complete moles reflects echogenicity of the massively hydropic villi. Since ready availability of beta human chorionic gonadotropin (β-hCG) assay and widespread adoption of obstetrical ultrasound, the classical (and generally late) presentation is now uncommon in the United States and other developed countries.[39] Consequently, the gestational age at presentation now often ranges from 8 to 12 weeks. In this earlier time frame, molar pregnancy often is suspected based on unusually high β -hCG levels (>100,000 mIU/mL), abnormal ultrasound findings (e.g. absence of an embryo or fetus, or suspicion of missed abortion), or after pathologic evaluation of a "failed" pregnancy. Thus, pathologic evaluation of abnormal early pregnancies is quite important[40,41].

Proposed Pathogenesis: After considerable investigation, the genetic and cell biological bases of molar gestations are broadly understood. Informed by these investigations, complete moles can be divided into two groups: androgenetic and biparental. Most complete moles are diploid, though a small number are tetraploid. Abnormal gene regulation due to aberrant DNA methylation provides the common mechanistic basis for both groups, as well as the basis for ancillary testing.

Diandry is the genetic condition in which a zygote contains two haploid genomes of paternal origin. Potential mechanisms by which diandry may develop include fertilization of a single oocyte by a diploid sperm, fertilization of a single oocyte by two haploid sperm, or duplication of the haploid paternal genome after oocyte fertilization. If the targeted oocyte is empty or the maternal haploid genome is extruded during the completion of meiosis, the product of fertilization is a diploid (2n) genome in which all the hereditary material is of paternal origin. Duplication of the paternal haploid genome, detectable as genome-wide homozygosity, occurs in about 80 percent of complete moles. The karyotype of such conceptuses is always 46,XX. Dispermy, resulting in genome-wide heterozygosity, occurs in almost 20 percent of complete moles, and such conceptuses may be either 46, XX or 46,XY. The lack of a maternal genome unmasks the phenomenon known as imprinting. Genomic imprinting is the epigenetic process that silences gene expression in a parent-of-origin specific manner. There are nearly 100 imprinted genes in the human genome. In the case of complete hydatidiform moles, imprinted alleles inherited from the father are silenced by DNA methylation and active alleles inherited from the mother are absent. These imprinted genes are critical for balancing placental and fetal development. When the abnormally imprinted zygote is both diploid and diandric, embryogenesis fails and unrestrained chorionic villous proliferation ensues. For comparison, the presence of a maternal genome in a triploid, diandric gestation results in an abnormal fetus and a partial molar placenta.

Biparental complete moles are exceedingly rare, but they are important because they provide deep insights into early developmental biology and the pathobiology of hydatidiform mole.[42-51] Biparentalism comes to light in women who have had complete moles in more than one pregnancy. In addition to appearing to "recur," a family history with an autosomal recessive pattern of inheritance may be elicited. Maternal mutations in the gene *NLRP7* at 19q13.4 have been implicated in recurrent molar pregnancies. *NLRP7* is highly expressed in oocytes and early human embryos. Mahadevan et al. report that reduced *NLRP7* alters chromatin reprogramming mediated by DNA methylation and accelerates trophoblastic differentiation[52].

More recently, abnormal villous proliferations resembling complete mole have been recognized (androgenetic biparental mosaicism / chimerism, see Chapter 9), requiring proposal of several unusual genetic mechanisms to account for their pathogenesis[26,53]. These unusual cases came to light based on heterogeneous p57 immunohistochemical staining between villous stromal cells and cytotrophoblasts. One genetic mechanism is formation of a chimeric gestation from normal and molar zygotes. An equally plausible alternative mechanism is genetic mosaicism after fertilization. Lewis et al. report that some such cases have clinical behavior like typical complete hydatidiform moles[53].

Finally, diandric uniparental disomy of chromosome 11 (the condition in which there are two chromosomes 11, but both are of paternal origin) may demonstrate villous morphology (and abnormal p57 immunohistochemical staining) resembling a hydatidiform mole[10]. Such exceptional cases highlight the relevance of the imprinted region on chromosome 11 in the underlying pathogenesis of complete hydatidiform mole.

Gross Features: Complete hydatidiform mole earns its Greek-based moniker for its well-known gross appearance. This classical appearance stems from the massive and diffuse swelling of chorionic villi to

Figure 4.5 Macroscopic image of grape-like villous swelling in a complete hydatidiform mole admixed with blood clot. The swollen villi of a complete mole are more uniform in both size and distribution compared to a partial mole.

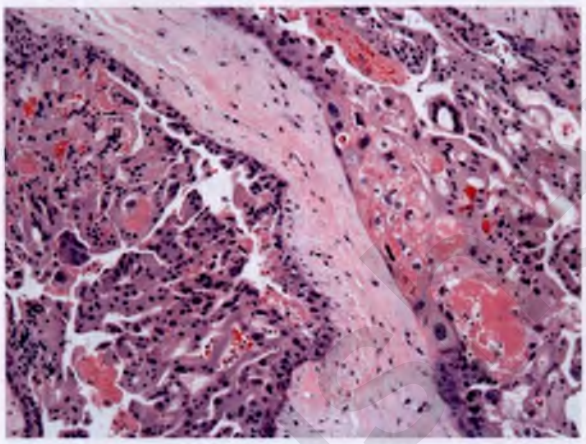

Figure 4.7 Microscopic image of florid, circumferential trophoblast hyperplasia and atypia in a complete hydatidiform mole.

form grape-like cysts of macroscopic size (Figure 4.5). Villous swelling and cavitation, however, is a progressive change, and villous enlargement may be rather subtle at earlier gestational ages. Villous architectural changes also may be masked by prominent, often degenerated blood clot.

Microscopic Features: Complete moles also exhibit a range of histological findings dependent on the gestational age. First, the uniformly large, hydropic villi notable during gross exam can be appreciated at low magnification on tissue sections. As the molar villi swell due to stromal degeneration and trophoblast proliferation, central cavitation is frequent

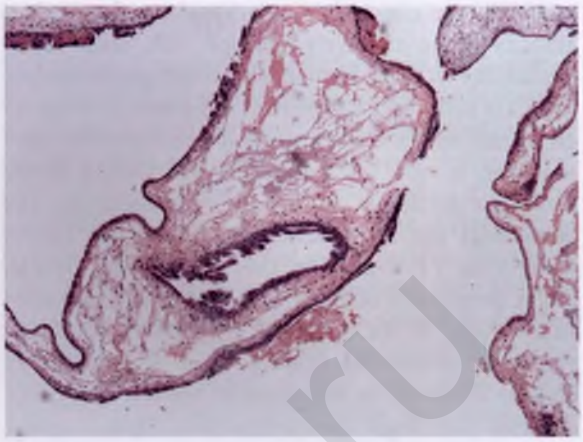

Figure 4.6 Microscopic image of grape-like villous swelling in a complete hydatidiform mole. Note the relatively (and uncharacteristically) minimal trophoblast hyperplasia and atypia in this case.

(Figure 4.6). The resultant cisterns are filled with clear or proteinaceous fluid. Extremely large, cavitated villi may be sheared or may burst, leaving only the cyst wall, which can mimic chorionic plate histologically. Circumferential trophoblast hyperplasia is present and often conspicuous (Figure 4.7). Exuberant intravillous-type extravillous trophoblast may form in lacy networks or filiform tags. Trophoblast atypia is common but variable. This range in atypia once provided the basis for histological grading, but the prognostic significance of molar grading in the chemotherapy era is no longer useful. Embryonic development is absent. Consequently, observation of fetal tissue requires consideration of other diagnostic entities, potentially including twinning with a complete mole (see below) and a partial hydatidiform mole. With rare exceptions, nucleated fetal red blood cells also are absent[54,55]. Of note, the first clue to the molar nature of a gestation may come from appreciating trophoblast atypia well beyond that typical in normal implantation site.

Development of the hydropic phenotype is progressive over gestation, and Keep et al. have described the histological features of an "early" complete mole[41]. Their villi are non-hydropic, but have characteristic shapes with scalloped or "knuckle-like" contours. The deep clefts of trophoblasts into the chorionic villous stroma have been described as resembling "popcorn," "cauliflower," and "toes on feet" (Figure 4.8). The stroma within early moles is remarkably hypercellular and composed of prominently blue myxoid

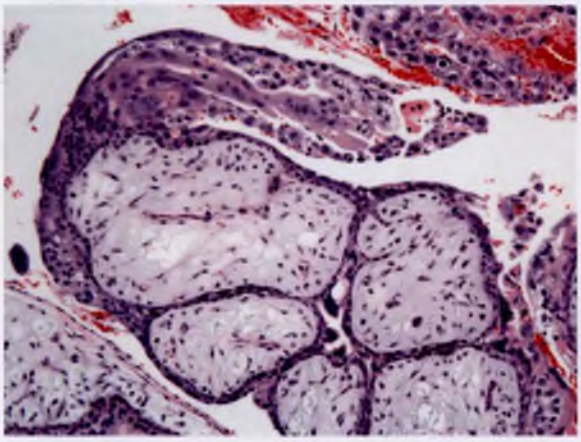

Figure 4.8 Early complete mole with deep trophoblast inclusions, which form finger-like projections, prominent blue myxoid villous stroma, and scattered stromal karyorhexis.

extracellular matrix (Figure 4.8). Single cell degeneration and karyorhexis is frequent among the villous stromal cells. In older examples, formation of small cystic cavities may be appreciated. Although well-formed blood vessels are absent, rudimentary vascular spaces may be seen. In most cases, these primitive capillary-like structures are empty because development of the yolk sac (and fetus) fails to occur. Unusual cases of complete moles, however, may have nucleated fetal red blood cells. Presumably, limited hematopoiesis takes place in the yolk sac in exceptional cases. Co-twinning with a molar gestation can also account for nucleated red blood cells. Trophoblast hyperplasia and atypia may be less obvious, as it can overlap with that seen in very early gestations. Recognition of atypical implantation site, which is severe in two-thirds of cases, may be helpful when present (see the molar implantation site illustrated in Figure 4.19, discussed below under exaggerated implantation site reaction/atypical implantation site)[15]. The key features of early complete mole are narrow cleft-like invaginations of the trophoblasts, prominent blue myxoid stroma, and frequent stromal cell degeneration[41].

Differential Diagnosis: The main differential diagnoses include partial hydatidiform mole, normal early gestation, hydropic abortus, and empty gestational sac. Partial moles may be distinguished from complete moles by the presence of biphasic villous morphology. Complete moles generally have uniform enlargement and shape abnormalities. If villi of normal size and shape are admixed with abnormally large and irregularly shaped villi, one must consider the possibilities of partial hydatidiform mole and twin gestation with both normal and complete molar conceptuses. Recognition of frequent nucleated red blood cells and absence of severe trophoblast atypia also should prompt consideration of these alternative diagnoses. In contrast, hydropic abortus often has uniformly swollen villi, but this change may be more regional when the entire specimen is inspected at low magnification. Furthermore, the swollen villi have more rounded contours (i.e. less complex villous shapes), no or minimal trophoblast atypia, and no trophoblast hyperplasia. The lack of trophoblast hyperplasia can be recognized at lower intermediate magnification by the ever-greater attenuation of cytotrophoblasts cytoplasm as individual villi expand in size, much like the skin of a balloon before it pops. Cavitation of hydropic abortus or other spontaneous pregnancy losses is also rather uncommon. The trophoblastic shell of normal early gestations and empty gestational sacs may mimic a cavitated molar villous, but can be recognized when one appreciates that there is only one such structure in a very small specimen. Early normal gestations may also have villous stroma that is more basophilic, and the syncytiotrophoblast and cytotrophoblasts may seem lusher than they do later in gestation. Lack of deep trophoblastic inclusions, forming "toes" or "popcorn," and healthy villous stromal cells are also clues leading one away from the diagnosis of a complete mole.

If in doubt, correlation with p57 immunohistochemistry or submission of additional tissue blocks for histologic examination may be helpful.

Ancillary Diagnostic Testing: When available, correlation with karyotype or newer advanced genomic testing may be productive, as most complete moles are diploid and partial moles are triploid.

There are several caveats that must be considered when interpreting karyotypic data. For example, uncommon tetraploid gestations with histological features approximating complete moles have been described[11,25]. Interestingly, other tetraploid gestations may have histological features and clinical behavior more like partial hydatidiform moles, perhaps reflecting triandric tetraploidy and the importance of the ratio of paternal and maternal genomes in determining the balance between fetal and placental development. Cases with aneuploid karyotypes (e.g. trisomy 11 or 13) may also be challenging, though their differential diagnosis is mostly with partial mole.

Another notable exception to the rule is diandric triploidy with loss of the maternal chromosome 11, which resulted in villous morphology and abnormal p57 staining mimicking a complete mole[56]. Though karyotype may be supportive, it is not diagnostic because one cannot ascertain the parental contributions.

Analysis of single nucleotide polymorphisms (SNP) by limited microsatellite PCR amplification, microarray, or extensive (whole genome or exome) sequencing may permit detection of genome-wide, copy number-neutral loss of heterozygosity, but is not possible to discern whether any such case is digynic or diandric without correlation with one or both parents[18]. The feasibility, cost-effectiveness, and practicability of advanced molecular diagnostic testing for the diagnosis of moles remains to be determined.

CDKN1 C, also known as p57 or KIP2, is one of the imprinted genes on 11p15.4 during early development. This gene (and others in the region) is expressed only from the maternal allele in cytotrophoblast. Castrillon et al.[57] correctly predicted that p57 silencing in complete hydatidiform moles, as they are the only purely androgenetic product of conception, could be exploited as a diagnostic test[57]. Immunohistochemistry for p57 stains the nuclei of cytotrophoblasts and villous mesenchymal cells. Thus, a "positive" result indicating the diagnosis of a complete hydatidiform mole can be declared when p57 staining is absent in cytotrophoblasts and villous stromal cells (Figure 4.9). Parental imprinting (silencing) of p57 is relaxed, permitting gene expression, in extravillous trophoblast and some syncytiotrophoblast, but this must not be taken as excluding a complete mole. p57 immunostaining is also found in maternal decidua, reflecting its biparental nature. Consequently, observation of p57 immunostaining in extravillous trophoblast and decidual stromal cells functions as an internal positive control when evaluating absence of staining in chorionic villi. Entities in the differential for complete mole (partial hydatidiform mole, hydropic abortus, early normal gestation) retain staining for p57. Of note, rare cases in which heterogeneous p57 immunostaining (i.e. p57 immunostaining in cytotrophoblast but not in villous mesenchyme, or vice versa) have been described. Chimerism and mosaicism have been suggested as possible mechanisms. Regardless of the mechanism, such anomalous p57 immunohistochemical staining results should prompt careful description and such

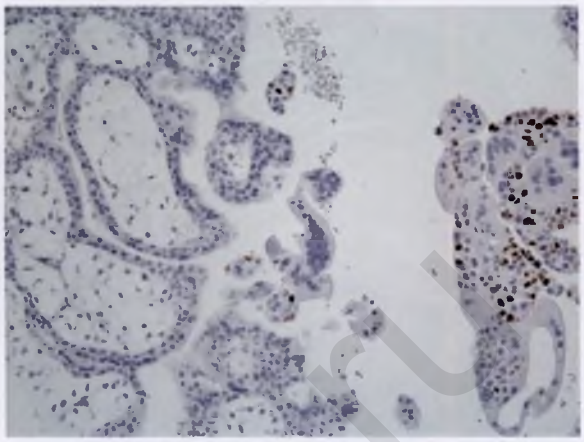

Figure 4.9 Immunohistochemical staining for p57 in an early complete mole. Note the absence of staining in the cytotrophoblast layer and villous stromal cells due to absence of a maternal copy of the p57 allele. Imprinting of p57 is relaxed in extravillous trophoblast (right); such relaxation of imprinting can be used as an internal positive control.

cases are probably best treated like a typical complete mole, as some previously reported cases have behaved so[53]. In sum, combining p57 immunohistochemistry with conventional histology effectively distinguishes a complete hydatidiform mole from common entities in the differential diagnosis and correctly flags unusual cases, even in the absence of data from other modalities.

Prognostic Implications: The reported incidence of trophoblastic malignancy after a complete hydatidiform mole ranges from 15 to 20 percent. Early detection by imaging or β-hCG monitoring has not altered this incidence, but earlier detection and lower β-hCG levels are favorable for the individual patient[58]. Malignant outcomes include invasive mole, metastatic molar pregnancy, and choriocarcinoma.

Contradictory to earlier thinking, histological grade or other microscopic parameters cannot be used in the post-chemotherapy era to predict which complete molar gestations will result in malignancy[59,60]. Outcome (and management) are, however, affected by many clinical and laboratory parameters. An interval between pregnancy recognition and uterine evacuation greater than four months is one adverse risk factor. Enlarged uterine size presumably is related to prolonged molar gestation. Serum β-hCG levels greater than greater than 100,000 or 40,000 mIU/mL units also is a poor prognosis factor for stage 1 or stage 2–4

Table 4.1 Revised and combined FIGO/WHO scoring system (FIGO 2000) for gestational trophoblastic neoplasia risk assessment*

FIGO Score	0	1	2	4
Age (year)	≤ 39	> 39	—	—
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	—
Interval (months) from index pregnancy	< 4	4 – 6	7 – 12	>12
Pretreatment hCG (mIU/ml)	$< 10^3$	$10^3 - 10^4$	$> 10^4 - 10^5$	$> 10^6$
Largest tumor size (cm), including uterus	3 – 4	≥ 5	—	—
Site of metastases	—	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1 – 4	4 – 8	> 8
Previous chemotherapy failure	—	—	Single agent	Multiple agents

* adapted from Kohorn[61]; after adding points assigned for each parameter, a low risk score is defined as ≤ 6, whereas a high risk score is ≥ 7.

disease, respectively. The brain and liver are frequent sites of distant involvement, and their involvement also portends unfavorable outcomes. These various parameters have been incorporated into a single system for risk assessment of gestational trophoblastic neoplasia (Table 4.1)[61]. In this system, a patient is deemed as having a low risk of malignant sequelae if the score is 6 or less, whereas a score of 7 or higher confers a high-risk status.

Low-risk molar pregnancies may be treated by uterine evacuation and monitored by serial serum β-hCG testing for at least 6 months after reaching undetectable levels, whereas patients with high-risk molar pregnancies may be offered prophylactic single chemotherapy (either methotrexate or actinomycin D). One clinically important consequence of β-hCG monitoring is the requirement for contraception and the inherent delay in fertility for couples urgent to conceive.

Although uterine evacuation is the mainstay of treatment for complete mole in most women, many leading gynecologic oncologists recommend a hysterectomy with ovarian preservation for women with hydatidiform moles who have completed childbearing and are 40 years of age or greater because of the higher risk of trophoblastic neoplasia in this group. A hysterectomy may also be required for emergent management of acute uterine hemorrhage prior to or at the time of molar evacuation.

Based on serum β-hCG monitoring, trophoblastic neoplasia can be diagnosed if the level plateaus (within 10 percent of the previous result) across 4 weekly measurements in a 3-week interval, increases more than 10 percent over a 2-week duration, or persists at detectable levels for more than 6 months following complete molar evacuation. Of course, histologic diagnosis of choriocarcinoma or an invasive mole as well as clinical or radiological evidence of metastasis also qualifies.

Single agent chemotherapy is highly effective for a complete hydatidiform mole and choriocarcinoma. Even when resistant to methotrexate, remission rates of 75 to 85 percent can be achieved with multi-agent chemotherapy[62].

The normal range of reproductive outcomes (including ectopic pregnancies, spontaneous abortions, stillbirths, premature deliveries, term live births, and congenital abnormalities) are found in pregnancies following complete hydatidiform mole, particularly for patients without subsequent β-hCG persistence or elevation, or patients who respond satisfactorily to methotrexate. The rate at which these various outcomes occur in subsequent pregnancies parallels the normal population[63–65]. Rates of repetitive hydatidiform mole in subsequent pregnancy have been estimated at between 1 and 2 percent, but rise to above 15 percent following a second molar pregnancy and should prompt medical genetic consultation to exclude the possibility

of familial inheritance, particularly due to *NLRP7* mutation[63–66].

Knowledge Gaps: Although much is now known about basic mechanisms, the specific genetic basis that accounts for the markedly increased risk in Asian women is poorly understood. In addition, whether a complete hydatidiform mole is due to silencing of a single gene (such as p57) or multiple genes is unknown. Finally, the molecular factors determining malignant behavior and resistance to chemotherapy need further investigation.

Invasive Hydatidiform Moles (*Chorioadenoma Destruens*)

Definition: An invasive mole is defined by the presence of molar villi invading myometrium or myometrial vascular spaces.[67]

Clinical Context: Given that curettage specimens do not usually include substantial portions of the myometrium, invasive mole cannot be reliably or practically diagnosed without a hysterectomy. It may be suspected when the curettage specimen is scant or based on high-resolution imaging of the uterus in the proper clinical context. It may be more frequent in women over 40 years of age and in underdeveloped countries[68].

Proposed Pathogenesis: The pathobiological basis accounting for the myoinvasive phenotype of invasive moles has yet to be elucidated.

Gross Features: Gross examination typically reveals a nodular hemorrhagic mass in the myometrium. Hemorrhage obscures its villous nature. Massively swollen villi may be observed within the myometrium or uterine cavity in some, but not all, specimens (Figure 4.10).

Microscopic Features: The histologic appearance of invasive mole consists of molar villi invading the myometrium or myometrial vascular spaces. The chorionic villi of invasive moles have the same trophoblast atypia and hyperplasia as that seen in their non-invasive complete molar counterpart. Molar villi may also invade into blood vessels and lymphatic spaces, accounting for the hemorrhagic macroscopic appearance. It is the conjunction of molar villi within the myometrium that directs one to the histological diagnosis.

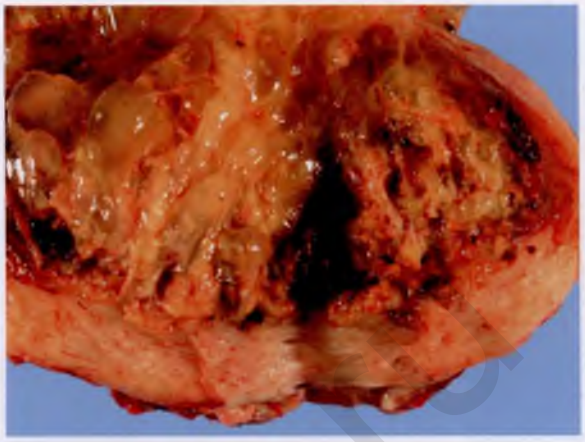

Figure 4.10 An invasive complete mole in hysterectomy specimen illustrates presence of cystic molar villi and invasion through an attenuated myometrial wall.

Differential Diagnosis: In some cases, villi may be relatively scarce and atypical trophoblast may be rather exuberant within the hemorrhage, potentially leading to an incorrect diagnosis of choriocarcinoma. The key distinction between an invasive mole and choriocarcinoma is recognition of villous formation.

Benign appearing placental parenchyma with grossly and microscopically normal chorionic villi appropriate to the gestational age should prompt consideration of some form of morbidly adherent placenta (e.g. placenta increta). In addition to the pathological features, morbidly adherent placenta tends to come to attention much later in gestation relative to invasive mole.

On rare occasions, placental involvement of existing myometrial defects (e.g. curettage and Cesarean section myotomy sites) may cause dehiscence of the uterine wall, which might be misinterpreted as chorionic villous invasion.

Ancillary Diagnostic Testing: Diagnosis of invasive mole is based on macroscopic and microscopic examination, and ancillary testing is of no benefit per se. That said, loss of p57 staining in villous cytotrophoblast and stromal cells is present in the invading molar villi, comparable to that seen in the typical complete molar gestation.

Prognostic Implications: Although invasive and metastatic molar pregnancies usually respond to chemotherapy, complications arising from local

hemorrhage at the invasive site may become clinically problematic, to the point that it requires hysterectomy.

Knowledge Gaps: The mechanistic basis for the greater chance of myometrial invasion by molar villi is unknown.

Complete Hydatidiform Mole in a Twin Gestation

Definition: This unique entity occurs when one gestation of dizygotic twins is a complete hydatidiform mole. The combination of normal and molar co-twins represents a pitfall because it is rare and can mimic partial hydatidiform moles in curettage specimens.

Clinical Context: The presence of a normal co-twin often delays diagnosis of molar gestation and is associated with higher pre-evacuation β-hCG levels and a greater risk to the mother for development of persistent gestational disease[69,70]. Consequently, symptoms such as vaginal bleeding, preeclampsia, hyperthyroidism, theca lutein cyst formation, and development of malignant trophoblastic neoplasia are all more likely. Such pregnancies also pose difficult obstetrical management issues when the normal co-twin is viable. Parents and the responsible clinical teams must balance the risks to the mother with those of the fetus, especially prematurity. However, successful, if not always term, pregnancies can be achieved.[71,72]

Proposed Pathogenesis: The genetic mechanism driving formation of the complete molar gestation in this entity is the same as that occurring in singleton pregnancies. The key distinguishing factor is fertilization of a second oocyte in the normal fashion. This can sometimes be proven when there is a discrepancy between their respective sex chromosomal complements[73].

Gross Features: Intact placental specimens show fused disks with well delineated areas of normal and molar placental parenchyma (Figure 4.11). Given that most samples will be collected by curettage, the normal and molar villi may be mixed and the admixture of normal villi with cystic molar villi can emulate a partial mole macroscopically. An intact fetus or fragmented fetal tissue may also be found. The 3–4 syndactyly and other anomalies characteristic of partial molar gestations would be absent in the normal twin. Absence of syndactyly alone, however, is not strong evidence for complete molar twinning.

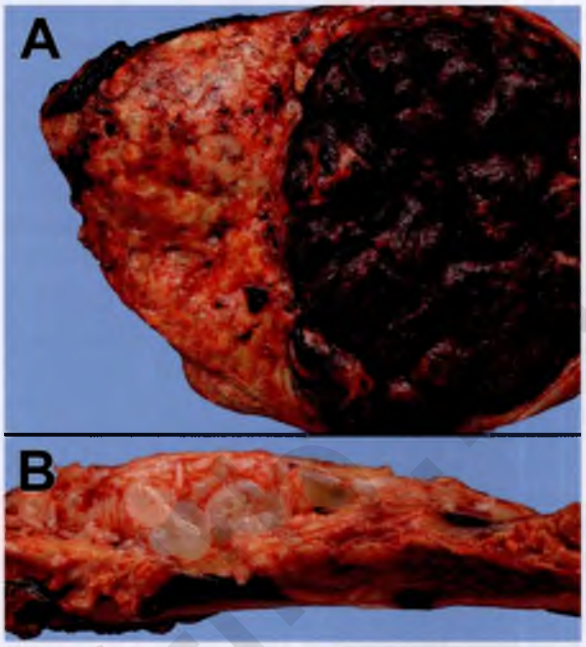

Figure 4.11 Twin placenta at term with a complete hydatidiform mole (left sides) and normal co-twin (right sides) show typical features in a well-demarcated fashion, as viewed from the maternal surface (a) and in cross-section (b). Specimens with a complete molar co-twin acquired by curettage, however, will be a mixture of normal and molar villi that may effectively mimic a partial hydatidiform mole.

Microscopic Features: Mimicry of a partial hydatidiform mole by this entity extends to microscopic examination. The extent of mixing varies. In most instances, villi from the normal twin will have a normal distribution of villous sizes and shapes, as well as minimal trophoblast hyperplasia and atypia. One, however, must be vigilant for cases in which the normal twin has failed and its villi have become enlarged due to edema (hydropic change). The molar villi have the same features as those in singleton complete molar gestations, though they may be more florid (e.g. greater cavitation) if evacuation has been delayed. There are two helpful clues that should prompt consideration of this entity. First, the normal and abnormal villi may not be distributed as uniformly as those seen in a partial hydatidiform mole. Second, the degree of histological derangement in complete molar villi is usually greater compared to most partial hydatidiform moles. For example, the trophoblast hyperplasia may

be more exuberant, the cavitation more frequent or extensive, or the implantation site more atypical.

Differential Diagnosis: The main consideration in the differential diagnosis is a partial hydatidiform mole, but one must consider other uncommon possibilities such as aneusomy, and mosaicism or chimerism. Twin gestations with a partial hydatidiform molar co-twin may also occur.

Ancillary Diagnostic Testing: The most helpful, if not essential, adjunct to histological evaluation is p57 immunohistochemistry. Normal cytotrophoblasts and villous stromal cells will retain expression of p57, whereas p57 staining is absent in cytotrophoblasts and villous stromal cells of admixed complete molar villi. If p57 immunohistochemistry does not clearly delineate two populations of villi in concordance with their histological findings, one should consider other possibilities.

Prognostic Implications: Delay in clinical recognition of twin molar pregnancy may increase the risk of persistent gestational trophoblastic disease[69,70].

Knowledge Gaps: The interaction between the normal and molar co-twins, particularly with respect to clinical presentation, is not well understood.

Choriocarcinoma

Definition: Choriocarcinoma is a multi-lineage trophoblastic malignancy composed of syncytiotrophoblast and mononuclear trophoblast resembling either cytotrophoblast or intervillous-type extravillous trophoblast. Though highly aggressive, choriocarcinoma is eminently curable.

Clinical Context: Choriocarcinoma is rare, occurring in 1 out of 20,000–40,000 total pregnancies[74]. In contrast, it has been estimated to occur in 1 out of 40 molar pregnancies[37,75]. Pregnancies preceding choriocarcinoma are in order of frequency: molar (>50 percent), preterm or term intrauterine (22.5 percent), spontaneously aborted (25 percent), and ectopic (~2.5 percent). The immediately antecedent pregnancy may precede the choriocarcinoma by months or even years, and is not necessarily the source of choriocarcinoma, particularly if there was a prior molar pregnancy[76,77]. Patients typically present with abnormal uterine bleeding and markedly elevated serum β-hCG levels after several months of pregnancy. Symptoms attributable to elevated β-hCG levels, such as hyperemesis, hyperthyroidism, and preeclampsia early in pregnancy, also may be present. When metastatic, the most likely sites are lung (90 percent) and brain or liver (20 percent to 60 percent). Consequently, presenting symptoms may be hemoptysis or neurologic abnormalities[78].

Proposed Pathogenesis: Choriocarcinoma evolving out of a molar gestation presumably represents autonomous overgrowth of the hyperplastic trophoblast, and reflects the underlying diandry. In contrast, choriocarcinoma developing from non-molar gestations reflects progression from intraplacental choriocarcinoma (see next section).

Gross Features: Gestational choriocarcinoma forms a well-circumscribed hemorrhagic mass within the uterus or rarely the fallopian tube.

Microscopic Features: Microscopic examination of choriocarcinoma shows a biphasic mixture of anaplastic syncytiotrophoblast and mononuclear trophoblast that may resemble cytotrophoblast, extravillous (intermediate) trophoblast, or both (Figure 4.12). Hemorrhage and necrosis are frequent and often prominent, reflecting the propensity for choriocarcinoma to invade blood vessels. A viable and histologically identifiable tumor is often found only at the periphery of a large hemorrhagic nodule near the tumor-host interface. Presence of villi should prompt consideration of alternative diagnoses, particularly complete

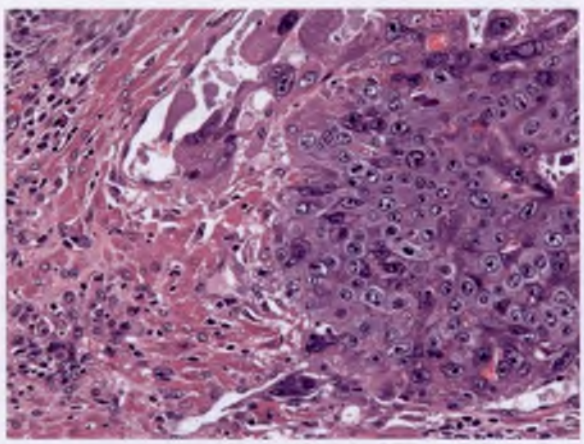

Figure 4.12 Choriocarcinoma present in a hysterectomy specimen bearing the pre-operative diagnosis of persistent gestational trophoblastic disease illustrates malignant syntiotrophoblast (center top) and cytotrophoblast (right) infiltrating myometrium (left).

hydatidiform mole or possibly intraplacental choriocarcinoma depending on the amount of villi present. Syncytiotrophoblast may have lesser cytologic atypia and no mitotic figures. Furthermore, syncytiotrophoblast may be focal or rare, but must be present to make a diagnosis of choriocarcinoma.

Differential Diagnosis: In very small biopsies, one might consider the possibility of residual benign trophoblast from a very early gestation, which can be suggested by a low serum β-hCG level. Based on gross examination, one might also consider the possibilities of an invasive mole, placental site or epithelioid trophoblastic tumor, and undifferentiated carcinoma. Presence of villi should redirect diagnostic consideration to a complete (or rarely partial) hydatidiform mole, intraplacental choriocarcinoma, and invasive mole. Exclusion of placental site and epithelioid trophoblast tumors is achieved by recognizing a biphasic cellular composition (including syncytiotrophoblasts), immunohistochemical expression of β-hCG without significant staining for either MelCam or p63, and high β-hCG serum levels (discussed below).

Ancillary Diagnostic Testing: Serum β-hCG as well as immunohistochemistry for GATA-3 (all trophoblast), β-hCG (only syncytiotrophoblasts), and MelCam and p63 (positive in placental site and epithelioid trophoblastic tumors, respectively), in the appropriate context, can be very helpful.

Prognostic Implications: Metastasis of choriocarcinoma to the fetus is rare (also see Chapter 22)[79, 80]. Choriocarcinoma represents a triumph of oncology, as more than 90 percent of patients can be cured by conventional single or multiagent chemotherapy. Chemotherapy may be more effective when choriocarcinoma is diagnosed early or with low serum β-hCG levels. Therapeutic decision-making for post-gestational choriocarcinoma typically is driven by the FIGO/WHO risk assessment score (Table 4.1)[61].

Knowledge Gaps: Details of the genetics of non-molar gestational choriocarcinoma as well as the features that might portend resistance to chemotherapy are largely unknown.

Intraplacental Choriocarcinoma

Definition: Intraplacental choriocarcinoma is, as the name implies, choriocarcinoma arising in the context of normal chorionic villi.

Clinical Context: Most cases are diagnosed in the third trimester, among asymptomatic women, and with a grossly normal placenta[81]. An unusual case arising in a partial mole has been documented[27]. Thus, histopathologic diagnosis is usually the first indication of intraplacental choriocarcinoma.

Proposed Pathogenesis: Unlike choriocarcinoma following a complete hydatidiform mole, little is known about the pathogenesis of its intraplacental, essentially *in situ*, counterpart. It is reasonable to presume that intraplacental choriocarcinoma is the precursor for most non-molar gestational choriocarcinomas, given that more than half of reported cases have been associated with metastatic disease[81].

Gross Features: The macroscopic manifestation of intraplacental choriocarcinoma mimics placental infarction. There may be hemorrhagic or tan-white, single or multiple scattered parenchymal nodules.

Microscopic Features: As lesions of intraplacental carcinoma are often small, low-power magnification allows identification of lesions distinct from the surrounding parenchyma (Figure 4.13). Highly atypical syncytiotrophoblast and cytotrophoblast fill the maternal intervillous space of the lesion, displacing normal villi. Occasionally, proliferating neoplastic trophoblast circumferentially cover villous stromal cores in a manner beyond the level seen in the

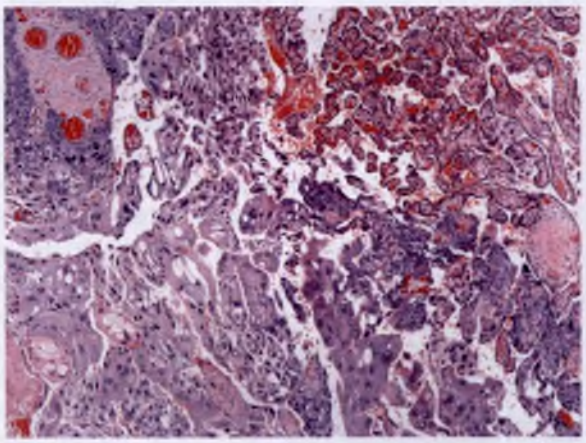

Figure 4.13 Intraplacental choriocarcinoma in a non-molar term placenta. This small non-villous neoplastic focus shows malignant syntiotrophoblast and cytotrophoblast juxtaposed to normal terminal villi (top right) in a term placenta.

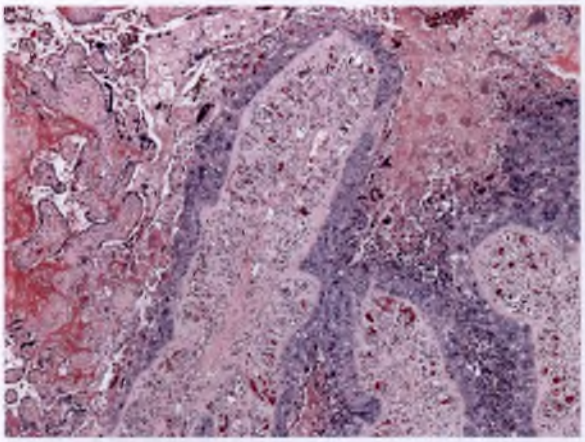

Figure 4.14 This intraplacental choriocarcinoma has malignant trophoblast associated with large club-like villi with chorangiomatous vessels and intervillous necrosis in the middle of an otherwise normal term placenta.

trophoblast hyperplasia of complete molar gestations (Figures 4.14).

Differential Diagnosis: Distinction from a complete hydatidiform mole with prominent trophoblast hyperplasia and atypia could be difficult in highly fragmented specimens. Histologic factors to be considered are the distinctness and size of the lesion. It may also be reasonably argued that diagnosis of intraplacental choriocarcinoma in a complete hydatidiform mole may be both semantic and clinically irrelevant. Maternal metastasis to the placenta by melanoma and breast carcinoma also form cellular intraplacental masses (see Chapter 22). Finally, at the macroscopic level, benign placental masses such as placental infarct might be included in the differential diagnosis, but conventional histologic examination will easily resolve the distinction.

Ancillary Diagnostic Testing: Follow-up with β-hCG monitoring is required. Other genetic tests are noncontributory for this entity.

Prognostic Implications: In one series, up to half of mothers had evidence of metastatic disease, usually at the time of delivery[81]. Fortunately, current chemotherapeutic regimens are highly effective, even in patients with metastatic disease.

Knowledge Gaps: The genetic etiology and relationship between intraplacental and conventional choriocarcinoma requires further study.

Extravillous Trophoblastic Lineage

Exaggerated Implantation Site Reaction / Atypical Implantation Site

Definition: Exaggerated implantation site is the histologically defined condition in which the implantation site trophoblast is more numerous or prominent in the endometrium and superficial myometrium than typically seen. Atypical implantation site is the condition in which the implantation site trophoblast have more nuclear and cytologic atypia than typical for implantation site.

Clinical context: In most cases, consideration of these entities arises following missed or spontaneous abortions prior to 20-weeks gestational age. Occasionally consideration follows gravid hysterectomies, usually for abnormal postpartum bleeding[82,83]. In either case, their recognition by pathologists prompts consideration of more serious diagnoses with overlapping histological features. Old implantation sites may persist for many months or several years after the antecedent pregnancy is complete and may be associated with abnormal uterine bleeding.

Proposed Pathogenesis: To understand the histological variations ranging from exaggerated implantation site to placental site trophoblastic tumor, it is helpful to have some understanding of the developmental biology of non-villous intermediate trophoblast (also see Chapter 1). Cytotrophoblast at the tips of early villi proliferate in a polarized fashion. Trophoblast cells at the surface of this proliferating cell mass furthest from the villous structure differentiate into implantation site trophoblast by expressing the cell adhesion molecule MelCam, also known as CD146 (Figure 4.15). Presence of this adhesion protein allows trophoblast to interact with endothelial cells and uterine smooth muscle cells, which also express MelCam. When MelCam-positive cells at the surface of this polarized trophoblast proliferation make contact with the endometrial surface, they migrate into the decidualized stroma. Shortly after beginning their migratory journey, this newly differentiated implantation site trophoblast ceases proliferating, thus becoming terminally differentiated.

It is not clear whether exaggerated implantation site represents a pathologic condition *per se*. In fact, most cases that appear to represent the extreme portion of the normal implantation spectrum. This notion

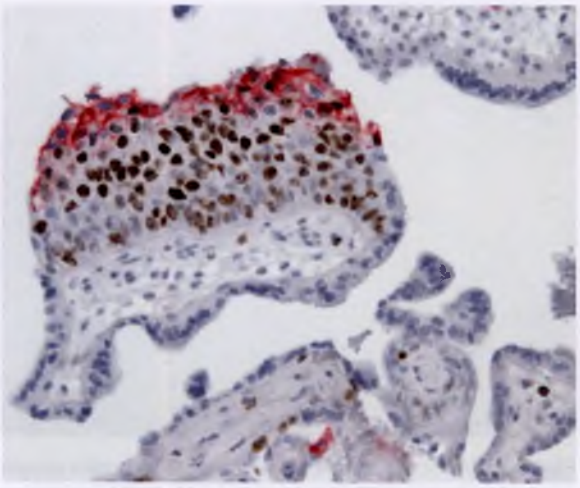

Figure 4.15 Implantation site trophoblast develop from areas of polarized cytotrophoblast proliferation extending from early villi that anchor on decidualized endometrium in the placental implantation site. This double immunohistochemical stain for the proliferation marker Ki-67 (with a brown staining product in a nuclear pattern) and cell adhesion molecule MelCam (also known as CD146; with a red staining product in a membranous pattern) shows the proliferation of these polarized cells. At the very tip of the proliferating cells, a shift in differentiation causes the concurrent expression of MelCam in double-positive cells. Trophoblasts migrating into the decidua cease proliferating but retain the MelCam expression, which facilitates interaction with endothelial and smooth muscle cells in the implantation site (not shown in this image, but is shown in Figure 4.17).

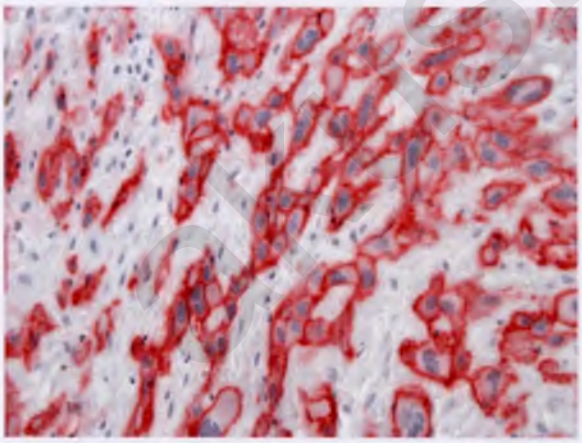

Figure 4.17 Exaggerated, non-neoplastic implantation site (same case as shown in Figure 4.16) is composed of implantation site trophoblasts with minimal atypia that stain for MelCam (CD146, shown in red) in a membranous pattern, but do not stain for Ki-67 (absent brown staining, counterstain is blue). For comparison to the staining pattern found in placental site trophoblastic tumor, see Figure 4.26.

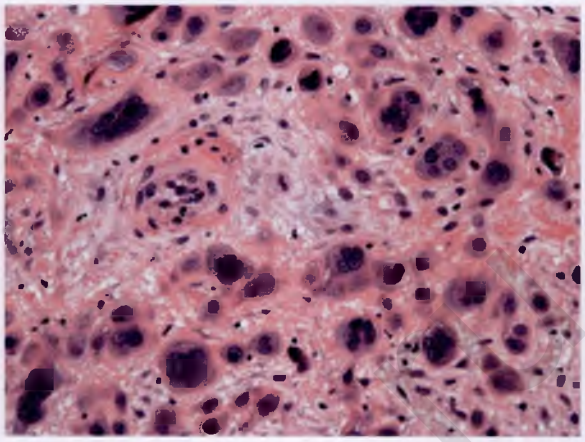

Figure 4.16 Exaggerated, non-neoplastic implantation site (same case as shown in Figure 4.17) with numerous multi-nucleated implantation site trophoblasts outnumbering decidualized stromal cells. Multi-nucleation of intermediate trophoblasts is more commonly found in the deeper portions implantation site, which reaches the superficial myometrium

is reinforced by the florid nature of implantation site trophoblasts very early in gestation. The pathogenetic origin of the atypical implantation site is unclear, and some pathologists have advocated for gathering more information about this histological condition.

Old implantation site, persisting as hyalinized nodules, result from a failure of the surrounding endometrium to properly terminally differentiate and shed at the end of pregnancy and subsequent menstrual cycles.

Gross Features: There is nothing unusual or specific for either entity, as both are histologically defined.

Microscopic Features: Exaggerated implantation site comes to mind when an unusual number or total volume of trophoblast is appreciated. The trophoblast, however, is not arranged in expansive or confluent sheets. Furthermore, the individual implantation site trophoblast have nuclear features overlapping with those seen in a normal implantation site. In other words, they lack the severe atypia of neoplastic trophoblast, even though they sometimes may be more frequently multi-nucleated or present at higher cell density compared with the average implantation sites (Figure 4.16). The trophoblast in this condition are not mitotically active, apart from the scattered foci near the contact point for anchoring chorionic villi (Figure 4.17). As in all implantation sites, some of the trophoblast in this entity will be intimately involved with the maternal spiral arterioles. Essentially,

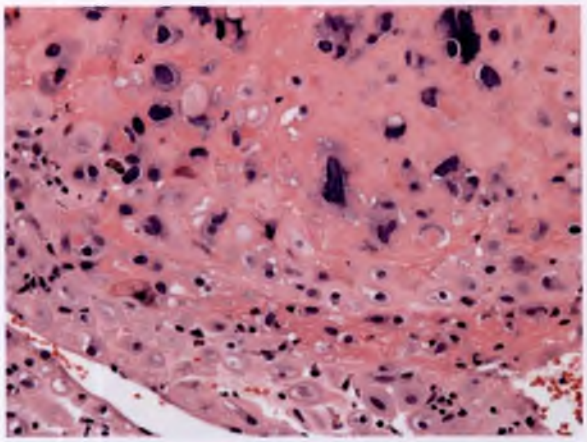

Figure 4.18 Atypical implantation site. Such nuclear atypia should raise concern for molar implantation site as well as placental site and epithelioid trophoblastic tumors.

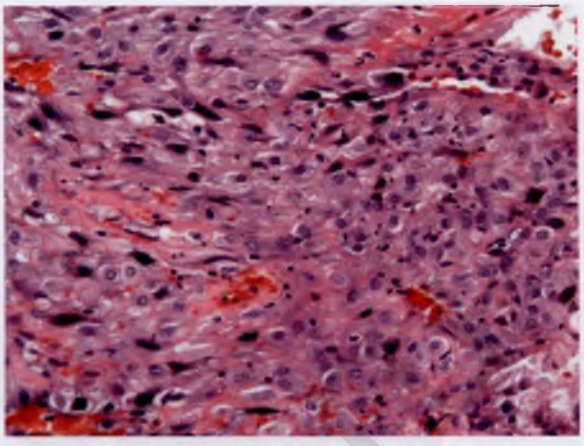

Figure 4.19 The molar implantation site often has greater nuclear atypia and pleomorphism than is typical for normal implantation (often visible at low magnification). The molar villi are not shown.

exaggerated implantation site is a more histologically lush variant of a normal implantation site.

Old implantation site consists of microscopic hyalinized nodules or plaques composed of implantation site trophoblasts embedded into inactive or proliferative endometrium. The trophoblasts have no atypia and in fact may become rather bland as they age.

Atypical implantation site is defined by having trophoblastic atypia far greater than ordinary implantation site. Such atypia comes in the form of greater nuclear size, angulation, chromatin coarsening and staining (Figure 4.18).

Differential Diagnosis: The lushness of implantation site trophoblast may provoke concern for placental site trophoblastic tumor. The latter is distinguishable by a more confluent, if not overtly destructively infiltrative, arrangement of atypical cells, often with numerous mitotic figures. If atypia is the more prominent histological aspect, the differential diagnosis should also include choriocarcinoma and molar implantation site. Often, significant atypia within the implantation site of a complete mole may be the first harbinger of a complete hydatidiform mole and should prompt a search for molar villi (Figure 4.19). If villi are scant, p57 and MelCam/Ki-67 immunohistochemistry can be helpful in excluding placental site and epithelioid trophoblast tumors.

Ancillary Diagnostic Testing: Although conventional histology is helpful, specific cases may benefit from review by an experienced placental pathologist. In a small number of cases, it may be helpful to confirm the trophoblast's non-proliferative nature. In our laboratory's experience, it is much easier and more reliable to assess mitotic activity by using a double immunostain with Ki-67 (with DAB as chromogen) and MelCam (CD146, detected with a red chromogen). The expected result for exaggerated or atypical implantation site is red membranes staining (confirming a cell as being an implantation site trophoblast) without nuclear staining (Figure 4.17). Cells that are double-positive for the proliferation and trophoblast marker should prompt concern for placental site trophoblastic tumor, and reevaluation of one's histological diagnosis. Finally, β-hCG is low or undetectable in old or involuting implantation sites, but may be positive with exaggerated implantation site.

Prognostic Implications: Though benign, exaggerated or atypical implantation sites may not shed properly and treatment should be dictated by clinical symptoms, such as abnormal uterine bleeding.

Knowledge Gaps: The key knowledge gap is the appreciation of the full spectrum of normal trophoblastic implantation site and the factors that determine it. The endometrial conditions that lead to improper clearance by menstrual shedding also are obscure.

Placental Site Nodule / Atypical Placental Site Nodule

Definition: Placental site nodules are hyalinized nodules or plaques derived from the trophoblast of

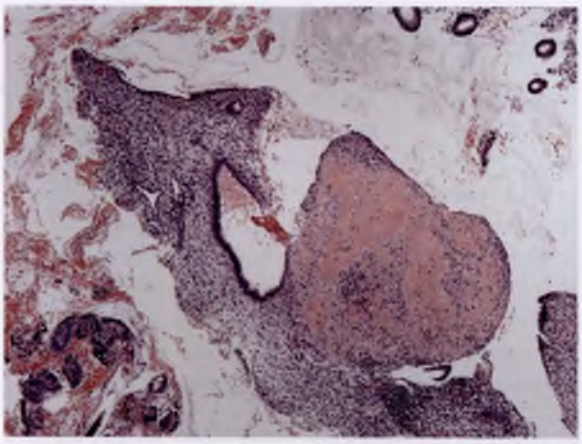

Figure 4.20 Placental site nodules, which may morphologically overlap with old or involuting implantation site, our composed of nodular or plaque like areas of collagen-rich stroma and variable numbers of cells embedded in non-gestational, often proliferative endometrium.

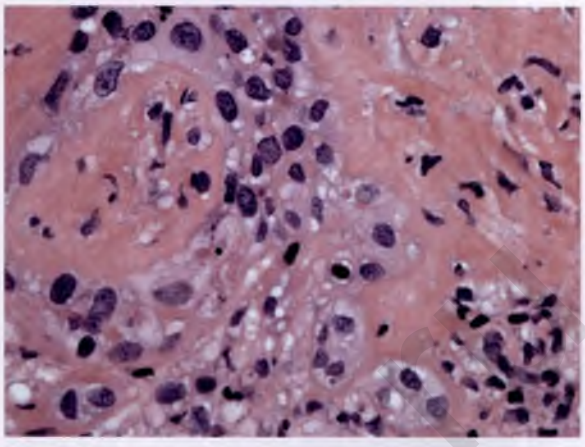

Figure 4.21 Placental site nodules have trophoblast with moderate amounts of eosinophilic, occasionally vacuolated cytoplasm arranged in small clusters or cords. Some pathologists make the distinction of placental site nodules from involuting implantation site based on the histological resemblance of the former to trophoblast found in the membranes of normal term placenta (see Figure 4.22 for comparison).

the placental membrane that persist after pregnancy. Atypical placental site nodules are similar apart from having a higher level of trophoblast atypia. Both are distinct from the exaggerated implantation site and involuting or old implantation site based on having extravillous trophoblast that are histologically and immunophenotypically similar to the mature extravillous trophoblast of the chorion laeve (i.e. membranous-type extravillous trophoblast), rather than like basal plate-type extravillous trophoblast found beneath the placental disk (see Chapter 5).

Clinical Context: Placental site nodules are common, though old implantation site nodules may be somewhat more so. Like old implantation site nodules, placental site nodules may be associated with abnormal uterine bleeding.

Proposed Pathogenesis: The proposed histogenesis is persistence or retention of microscopic portions of the chorion laeve and associated trophoblast[84]. Some placental site nodules appear to have transformed into ETT[83,85]. The notion that placental site nodules and epithelioid trophoblastic tumor develop from the mature extravillous trophoblast found in the placental membranes is further supported by their common immunophenotype[86,87]. Interestingly, placental site nodules differ from epithelioid trophoblastic tumor in that they lack the preponderance of XX genotypes found in epithelioid trophoblastic tumor[88,89].

Gross Features: There is nothing unusual or specific for either entity, as both are histologically defined.

Microscopic Features: Placental site nodules are often found in the context of inactive or proliferative endometrium (Figure 4.20). The nodules and plaques, which are often quite discrete, consists of clusters and loose cords of cells at moderate or low density and a hyalinized extracellular matrix. Fibrin, which characterizes recent or active pregnancy, is absent. The trophoblast present in the nodules have vaguely squamoid features with moderate eosinophilic or vacuolated cytoplasm and modest nuclear and chromatin changes (Figure 4.21). The nuclear features may become blander as the nodules age. Mitotic activity is characteristically absent. Overall, the cytologic features of trophoblast in placental site nodules closely resemble those found in second or third trimester placental membranes (Figure 4.22).

Differential Diagnosis: The distinction between placental site nodule, exaggerated implantation site, and old implantation site (differing only by the type of benign trophoblast present) is trivial. Presence of Nitabuch's fibrin points to presence of a current pregnancy with an exaggerated implantation site. The most important entity in the differential diagnosis, epithelioid trophoblast tumor, can be distinguished by presence of higher atypia and proliferative activity,

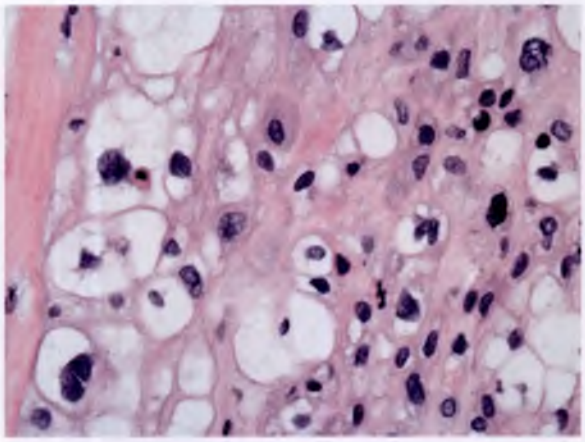

Figure 4.22 A distinct subset of non-villous trophoblast is present in the membranes of normal placentas (membranous-type extravillous trophoblast). These trophoblast demonstrate two related histological phenotypes, one with quite vacuolated cytoplasm and the other with squamoid features due to their moderately abundant eosinophilic cytoplasm.

manifested as a Ki-67 staining index greater than 10 percent in epithelioid trophoblastic tumor.

Ancillary Diagnostic Testing: Placental site nodules have the same immunophenotype as membranous-type extravillous (i.e. chorion leave) trophoblast, expressing p63 diffusely and MelCam (CD146) in scattered cells[84]. The Ki-67 staining index is less than 10 percent, but care must be exercised to verify that only trophoblasts are being evaluated. Serum β-hCG is low or undetectable in this entity.

Prognostic Implications: Some cases may be associated with abnormal uterine bleeding, which often resolves with the curettage used to make the diagnosis. Placental site nodules are otherwise benign in the majority of cases[90], though transformation into epithelioid trophoblast tumors has been reported[85].

Knowledge Gaps: The endometrial conditions that predispose to retention of implantation site nodules as well as the genetic changes that may predispose to progression to epithelioid trophoblastic tumor are unknown.

Post-Cesarean Epithelioid Trophoblastic Lesion

Definition: Post-cesarean epithelioid trophoblastic lesion is an enigmatic entity involving the proliferation of atypical epithelioid trophoblast, which forms a cystic mass penetrating the lower uterine segment in patients who previously have undergone cesarean section.

Clinical Context: This extremely rare entity is intrinsically linked to prior cesarean section. Whether there are other predisposing conditions is unclear. Some patients present with lower abdominal pain and persistent, irregular vaginal bleeding, and others have presented with cyclical hematuria.[91–94] Imaging or surgical exploration reveals cystic lesions in the anterior lower uterine segment, often accompanied by fistula formation or dehiscence of the prior cesarean section myotomy. One patient had a uterovesical fistula.

Proposed Pathogenesis: The pathologic appearance suggests a process that is a hybrid of an atypical placental site nodule or epithelioid trophoblastic tumor with dehiscence of the anterior lower uterine segment at the cesarean section scar, but the pathological mechanism is unknown.

Gross Features: The lesions are typically located in the anterior uterine segment and consist of a cystic mass or uterine diverticulum that may extend to or beyond the serosal surface.

Microscopic Features: The cystic mass has spaces lined by atypical epithelioid trophoblast with abundant eosinophilic cytoplasm, occasionally multiclefted or hyperchromatic nuclei resembling the cells found in the chorion leave, placental site nodules, and epithelioid trophoblastic tumors. Although the cells may penetrate deeply through the uterine wall, they do not destructively infiltrate the adjacent uterine stroma. Thus, the overall configuration resembles a diverticulum or dehiscence of the prior cesarean section myotomy by a cystic proliferation vaguely resembling placental membrane.

Differential Diagnosis: The differential diagnosis includes a lower uterine segment pregnancy implanting into the cesarean section scar (see Chapter 28) and epithelioid trophoblastic tumor. Determination of proliferative activity as well as severe nuclear and cytologic atypia, destructive invasion, solid mass formation, and calcification would favor the diagnosis of epithelioid trophoblastic tumor.

Ancillary Diagnostic Testing: Little is known about the contribution of ancillary testing to the diagnosis of this entity, but confirmation of the cellular immunophenotype using p63 and Ki-67 immunohistochemistry may be reassuring.

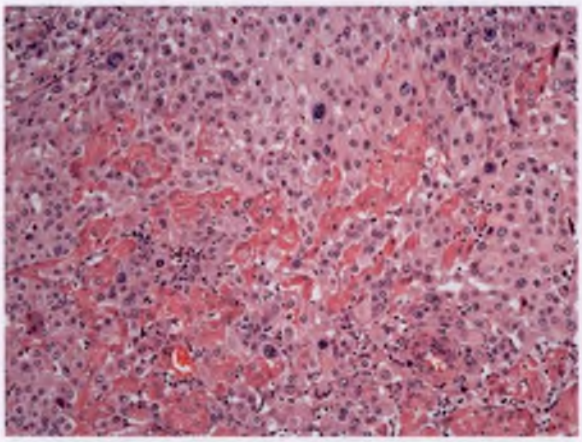

Figure 4.23 Placental site trophoblastic tumor is characterized by the sheet-like proliferation of moderate to abundant epithelioid or amphiphilic cytoplasm, often destructively infiltrating through the superficial myometrium.

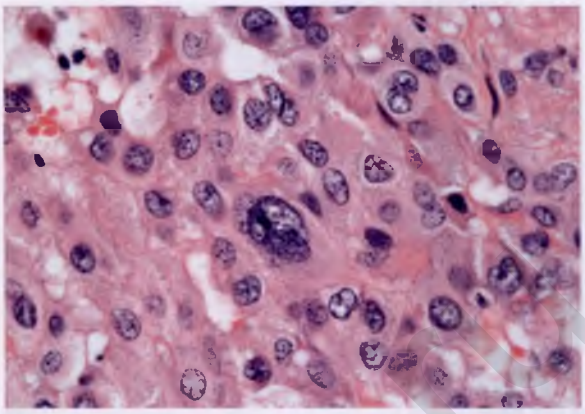

Figure 4.24 Placental site trophoblast tumor cells often have atypia exceeding that customary for trophoblast in normal implantation site.

Prognostic Implications: Although cases reported to date generally have had good outcomes following surgery removing the cystic mass and repairing any uterine wall defects, it is hard to have high confidence in prognostication given the extreme rarity of this entity.

Knowledge Gaps: The pathologic etiology, the relationship to prior cesarean section, and the natural history, particularly regarding the potential for malignant transformation, for post-cesarean epithelioid trophoblastic lesions are poorly understood.

Placental Site Trophoblastic Tumor

Definition: A placental site trophoblastic tumor (PSTT) is a mass-forming and infiltrative neoplastic proliferation of trophoblastic cells histologically and immunophenotypically resembling normal extravillous trophoblast in the placental implantation site[95,96].

Clinical Context: Although PSTT occasionally follows miscarriage, elective terinations, or other abnormal pregnancies, roughly two-thirds of cases are seen in reproductive-age women following a normal term delivery[88]. Uncommonly, PSTT also may present in postmenopausal women. The interval between the previous pregnancy and tumor presentation may range from many months to years. The typical presentation is vaginal bleeding, like that seen following a missed abortion. This clinical impression may be reinforced by the minimal elevation of serum β-hCG.

The primary therapy is hysterectomy because this tumor is relatively refractory to the chemotherapy typically used for trophoblastic neoplasia. Hysterectomy may be attempted when uterine conservation and preservation of fertility are desired.

Proposed Pathogenesis: PSTT has a pathogenesis distinct from that of hydatidiform moles. Curiously, both PSTT and epithelioid trophoblastic tumor arise primarily from female pregnancies[88,97,98]. The skewed distribution of sex chromosome composition contrasts with exaggerated placental site reaction, which has an equal distribution of XY and XX genomes[99]. Consequently, most exaggerated placental sites may not at risk for PSTT. The genetic mechanism by which diploid female genomes develop into PSTT is unknown, but some have a suggested that an active paternal X chromosome may be important[97].

Gross Features: PSTT typically manifests as a discrete mass involving the inner uterine wall. It may be either exophytic or endophytic.

Microscopic Features: The tumor consists of sheets of large polyhedral cells with ample cytoplasm and large atypical nuclei. The key distinction between PSTT and implantation site is the tumor's destructive nature, which forms confluent sheets as it infiltrates between the outnumbered myometrial cells (Figure 4.23). In most cases, the resemblance to early implantation site trophoblast is obvious, although many PSTT have atypia greater than seen in normal implantation site (Figure 4.24). In addition to atypia, mitotic activity distinguishes PSTT from normal implantation site (Figures 4.25 and 4.26). The mitotic rate may be variable, ranging from only

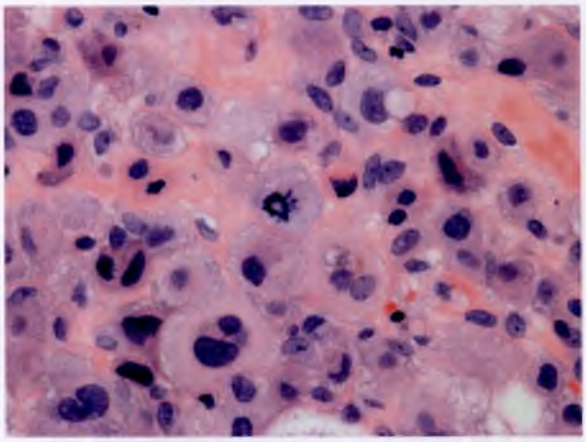

Figure 4.25 In contrast to normal implantation sites, mitotic figures are present and may be quite frequent in placental site trophoblastic tumors. In this instance, mitotic figures frequently were atypical, as illustrated by the ring mitoses at center.

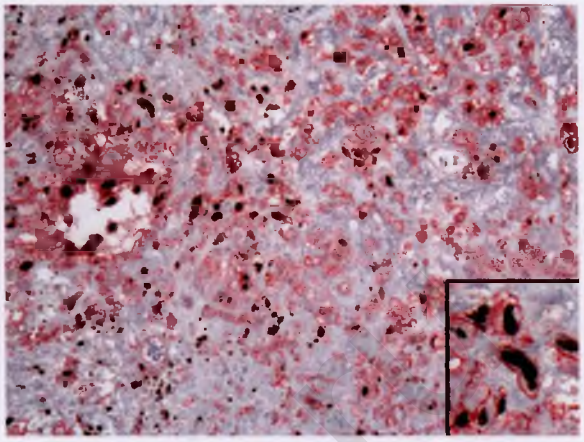

Figure 4.26 The most useful stain in arriving at the diagnosis of a placental site trophoblastic tumor involves double immunohistochemistry for MelCam (CD146), detected by red staining product, and Ki-67, detected by brown staining product. Implantation site trophoblast, in contrast to most of the extravillous trophoblast in the placental membranes, express the cell adhesion molecule MelCam in a membranous pattern. Double immunohistochemistry is diagnostic for a placental site trophoblastic tumor when double-positive (so called "bull's-eyes") cells, which represent proliferating implantation site trophoblasts, are identified (inset). Normal implantation site lacks such proliferative activity (see Figure 4.17 for comparison).

a few mitotic figures per 10 high-power fields up to over 30 per 10 high-power fields. Tumor necrosis also distinguishes PSTT from normal implantation site, though one must be careful not to over interpret necro-inflammatory changes in the endometrium and implantation site associated with ischemia and placental separation.

Differential Diagnosis: Placental site nodule is the most often discussed entity in the differential diagnosis with PSTT, but epithelioid trophoblastic tumors, choriocarcinoma, and molar implantation sites as well as undifferentiated carcinomas and sarcomas must also be considered. Immunochemistry is particularly helpful both in terms of confirming the increased proliferative rate and histotyping the constituent trophoblast.

Ancillary Diagnostic Testing: GATA-3 immunostaining is now the best single marker to confirm the trophoblastic nature of the uterine mass[100,101]. PSTT are positive for MelCam, human placental lactogen and inhibin, and negative for p63[87]. MelCam (CD146, MUC18) is a cell surface adhesion molecule expressed strongly by vascular endothelial cells, smooth muscle cells, and normal implantation site trophoblast. In this author's opinion, the most useful immunohistochemical technique for diagnosing PSTT is a double stain that detects membranous MelCam expression (usually with a red chromogen) and nuclear Ki-67 expression (usually with a brown chromogen). The staining pattern in normal implantation site shows only the membranous staining, but PSTT shows double staining with a round red circle with a brown bull's-eye (Figure 4.26). The Ki-67 proliferative index should be 10 percent or greater. Care must be exercised if Ki-67 staining is performed as a single stain so as not to count proliferation of inflammatory or endometrial stromal cells. If the tumor is positive for nuclear p63 staining, one should consider placental site nodule or epithelioid trophoblastic tumor. Strong staining for β-hCG would be more typical of a choriocarcinoma, though sporadic staining may be seen in some PSTTs.

Of import, serum β-hCG levels do not reflect tumor burden. If serum β-hCG is high, consideration of choriocarcinoma or molar disease is required.

Prognostic Implications: Clinical behavior of PSTT is heterogeneous.[102,103] About one-third of patients will develop recurrent disease. The risk of recurrence is higher when the interval between the antecedent pregnancy and tumor is greater than 2 years. Investigators at Charing Cross Hospital report that the 5-year survival rate for PSTT is 80 percent[104]. The modified and combined FIFO/WHO scoring system (Table 4.1[61]) for gestational trophoblastic disease does not correlate with outcome, but lung

metastasis and antecedent pregnancy of 4 years or greater are adverse prognostic factors, and disease confined to the uterus is a favorable prognostic factor[105]. The only histologic parameter thought to be prognostically relevant is mitotic activity; mitoses numbering less than 5 per 10 high-power fields is associated with a more favorable outcome[106]. Hysterectomy is the therapy of choice for disease confined to the uterus, and chemotherapy combined with surgery is used for patients with extrauterine disease.

Knowledge Gaps: Although much remains to be learned about PSTT, the genetic basis of this rare trophoblastic tumor and targets for directed chemotherapy are of greatest interest.

Epithelioid Trophoblastic Tumors

Definition: Epithelioid trophoblastic tumor (ETT) is a neoplastic proliferation of extravillous trophoblast distinct from those present in the implantation site and intervillous space[95,96]. The non-neoplastic counterpart present in ETT is thought to be trophoblast in transition from villous cytotrophoblast to mature extravillous trophoblasts found in the placental (chorionic) membranes[84]. The basis of this supposition is that an ETT has histological and immunophenotypic features similar to trophoblast in the chorionic membrane (chorion leave).

Clinical Context: Like placental site trophoblastic tumor, ETT is a rare mass-forming trophoblastic tumor, occurring primarily in the uterus and usually affecting reproductive-age women. Most cases of ETT follow term pregnancies, and the interval between the antecedent pregnancy and tumor presentation may vary from months to years. Patients often present with irregular vaginal bleeding, and the initial clinical impression may be that of missed abortion. Accordingly, β-hCG levels are minimally elevated. Cervical involvement by ETT is not uncommon and its resemblance to squamous cell carcinoma may challenge the unsuspecting pathologist[107]. Also of import to pathologists, an ETT may present as an extrauterine process, possibly due to peritoneal dissemination of trophoblasts during cesarean section[108].

Proposed Pathogenesis: Although little is known about the pathogenesis of ETTs, their mechanism is distinct from hydatidiform mole and may be similar to PSTT based on the preponderance of XX genotypes in ETTs[88,89]. Some placental site nodules appear to have transformed into ETT[83,85]. The notion that placental site nodules and ETTs develop from the mature non-villous trophoblast found in the placental membranes is supported by their common immunophenotype[86,87].

Gross Features: ETTs generally are solitary, circumscribed solid masses invading myometrium or cervical stroma. Hemorrhage or calcification may be prominent in some tumors. Chorionic villous architecture is absent.

Microscopic Features: The neoplastic trophoblast in ETT are typically medium-sized epithelioid cells with abundant eosinophilic cytoplasm and monomorphic, mostly bland (relative to other neoplastic trophoblasts) nuclei (Figure 4.27)[109]. Some neoplastic ETT cells may be vacuolated. Both the vacuolated and non-vacuolated epithelioid cells resemble normal trophoblast in the chorionic membrane. The neoplastic trophoblast of ETT are usually arranged in small clusters, nodules or cords, but occasionally may form more expansile sheets. ETT cells may grow in association with hyalinized eosinophilic extracellular matrix. In addition, necrotic debris or calcification may be present at the center of the clustered or corded tumor cell aggregates (Figure 4.28). Such cellular arrangement, particularly in association with calcification or debris, may strongly resemble

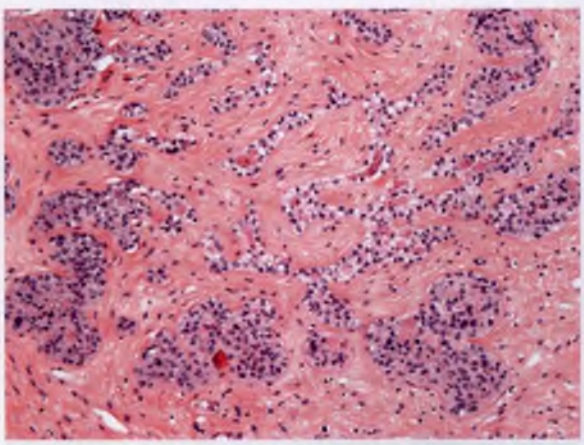

Figure 4.27 The neoplastic cells of epithelioid trophoblastic tumors are arranged in small nests and cords of epithelioid cells with moderate epithelioid or vacuolated cytoplasm and moderately atypical nuclei.

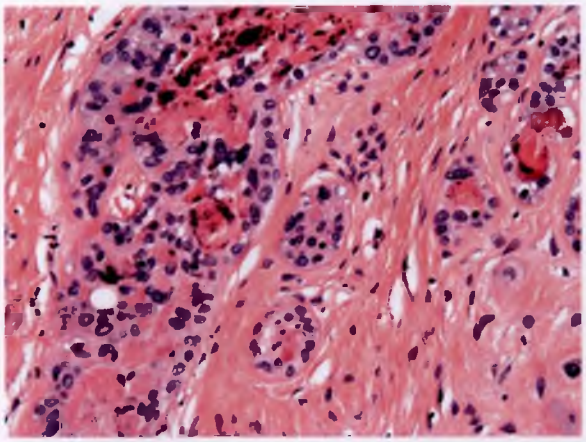

Figure 4.28 Epithelioid trophoblastic tumors sometimes resemble invasive squamous cell carcinoma because of their squamous-like cytologic features and necrosis occurring in the center of clustered cells that resembles keratinization.

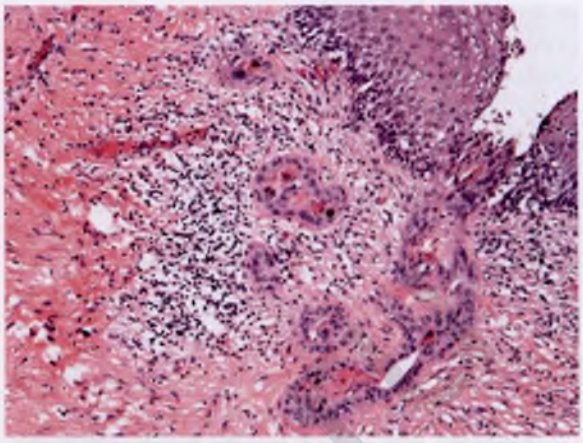

Figure 4.29 Epithelioid trophoblastic tumors occurring in the cervix are particularly problematic because they mimic primary squamous cell carcinoma.

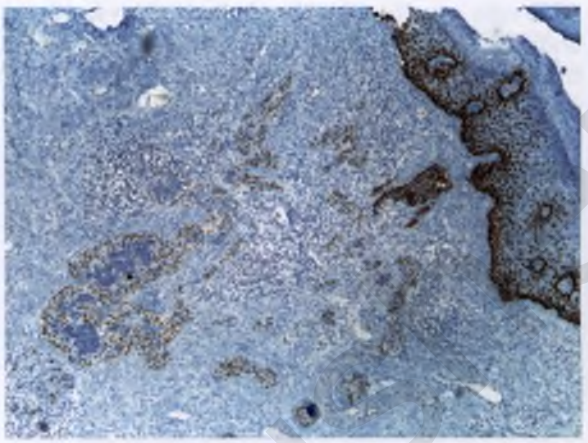

Figure 4.30 Further complicating the distinction of an epithelioid trophoblastic tumor from squamous cell carcinoma is the fact that both express p63 (note: positive basal squamous epithelium on right and nests of ETT on left).

neoplastic squamous epithelium in cervical biopsies. The presence of higher levels of atypia does not exclude the possibility of ETT. Mitotic activity is low relative to other neoplastic trophoblastic proliferations, but it is significantly elevated relative to normal extravillous trophoblast.

Differential Diagnosis: As noted above, ETT presenting in cervical biopsy specimens can mimic preinvasive and invasive squamous neoplasia (Figure 4.29). Arrival at the correct diagnosis may be facilitated by immunohistochemistry (Figure 4.30). The differential diagnosis for ETT also includes benign placental site nodule, epithelioid leiomyosarcoma, and PSTT. Benign placental site nodules are usually seen in the context of a current or recent pregnancy, usually accompanied by decidualized endometrium and have no proliferative activity (Ki-67 staining indices of 10 percent or less). They are microscopic lesions showing hyalinization and variable inflammation, but lack central necrosis. In contrast, ETTs have variable, but definitively elevated, proliferative rates and form distinct masses. Epithelioid leiomyosarcoma and PSTTs may be more challenging to diagnosis, but immunohistochemistry is often helpful.

Ancillary Diagnostic Testing: Immunohistochemistry is the most helpful tool after conventional histology. ETTs are positive for GATA-3 and p63, both with nuclear staining patterns (Figure 4.30)[87,100,101]. Of note, squamous epithelial lesions will be positive for keratins and p63, but are usually negative for GATA-3. Unlike PSTT, ETT cells are negative or less commonly positive in a patchy or focal fashion for MelCam (CD146) and human placental lactogen (hPL) staining. ETTs are also positive for inhibin and keratins, but these are usually second-line stains. The Ki-67 proliferative index should be 10 percent or greater.

Prognostic Implications: ETTs show a wide range of biological behavior[110]. Many cases can be treated with hysterectomy alone. Extrauterine ETT, however, may be aggressive and refractory to conventional chemotherapies. Mitotic rates greater than five mitoses

per 10 high-power fields and presentation more than a few years after the last known pregnancy may be adverse prognostic factors.

Knowledge Gaps: Although much remains to be learned about ETT, the genetic basis of this rare trophoblastic tumor and targets for directed chemotherapy are of greatest interest.

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Chapter 5

Maternal Vascular / Trophoblastic Developmental Abnormalities

Raymond W. Redline

The primary function of trophoblast is to interact with maternal tissues to establish adequate placental attachment and access to maternal arterial blood flow. Maternal trophoblastic lesions of the placenta can be separated into three subgroups: those related to abnormal early maternal-trophoblastic interaction (developmental abnormalities; this chapter), those consequent to later inadequate blood flow (maternal vascular malperfusion; Chapter 7), and those due to premature uteroplacental separation, often involving an abnormally implanted placenta (loss of maternal vascular integrity; Chapter 8). A fourth process, distal villous hypoplasia, incorporates aspects of both maldevelopment and malperfusion, and is discussed separately in Chapter 6. Developmental abnormalities can reflect either intrinsic abnormalities in the trophoblast or abnormal crosstalk between trophoblast and the mother.

Superficial Implantation Site (Shallow Implantation, Persistent Muscularization of Basal Plate Arteries, Increased Placental Site Giant Cells, Excessive Implantation Site Trophoblastic Giant Cells)

Definition: Failure of the extravillous trophoblast (EVT) to adequately invade the myometrium and remodel the spiral arteries as reflected by persistent muscularization (and/or atherosis) of basal plate arteries and excessive numbers of placental site giant cells in the basal plate.

Clinical Context: Superficial implantation was first described in the placentas of patients with preeclampsia – particularly preterm, severe, and/or associated with fetal growth restriction (FGR)[1]. It may also be seen in cases with normotensive FGR (especially with abnormal pulsed flow Doppler testing), underlying cardiovascular risk factors, and autoimmune diseases[2,3].

Proposed Pathogenesis: Intrinsic (e.g. abnormal protease/antiprotease function) and extrinsic abnormalities (e.g. tissue hypoxia, altered renin-angiotensin system activity, antiphospholipid antibodies) retard the normal maturation and function of EVT, resulting in failure to invade the superficial myometrium and adequately remodel the spiral arteries that supply the intervillous space[4–7].

Gross Features: Superficially implanted placentas are often small for gestational age and have an increased fetoplacental weight ratio[8]. Macroscopic lesions such as villous infarcts and perivillous fibrin plaques are common. Some authors have found an association with decreased placental diameter, increased placental thickness, elongation (increased maximum–minimum diameter), thin umbilical cord, and peripheral umbilical cord insertion (see Chapter 16).

Microscopic Features: The strongest histologic evidence of superficial implantation is persistence of vascular smooth muscle within basal plate arteries in a non-marginal section from a placenta of more than 24 weeks (Figure 5.1). By the middle of the third trimester, maternal spiral arteries in the basal plate should be completely "remodeled" as defined by dilatation, loss of vascular smooth muscle, and replacement of smooth muscle by EVT and its secretion products: laminin, fibronectin, type IV collagen, and entactin (collectively known as "matrix-type fibrinoid"). This process is also known as "physiologic change" or "fibrinoid replacement". A common error is to confuse the term "fibrinoid replacement" with "fibrinoid necrosis". Basal plate arteries with fibrinoid replacement are lined by pink flocculent material, lack smooth muscle, show marked luminal dilatation, and contain scattered intramural EVT (Figure 5.2). Those with fibrinoid necrosis have glassy, deep-red staining of necrotic smooth muscle,

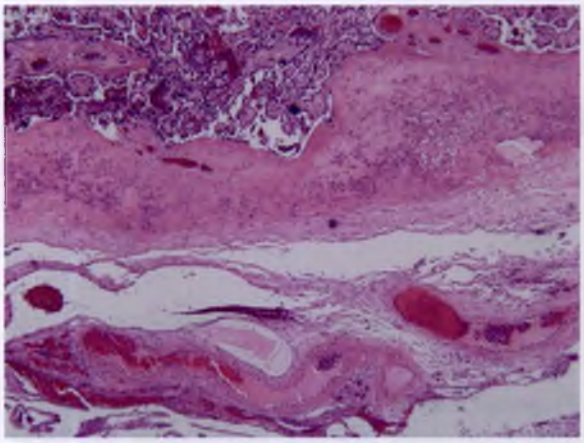

Figure 5.1 Abnormal persistence of vascular smooth muscle in basal plate arteries: narrow, muscularized spiral arteries are seen in the loose decidua underlying Nitabuch's layer. Image provided with permission by R. Redline, University Hospitals Cleveland Medical Center, Cleveland, OH.

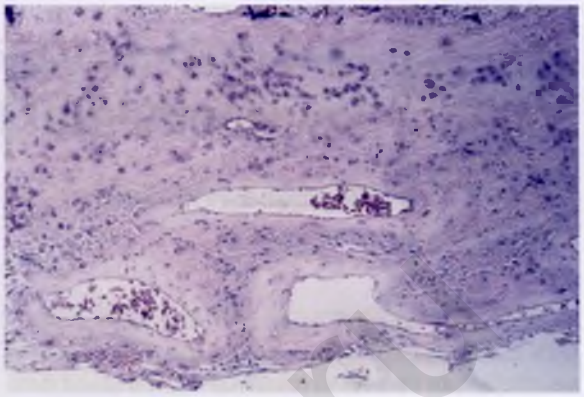

Figure 5.2 Normal replacement of the vascular smooth muscle of basal plate arteries by fibrinoid matrix ("physiologic change"): dilated spiral artery segments show scattered intramural endovascular extravillous trophoblast, an abundant secreted flocculent pink fibrinoid matrix, and an absence of vascular smooth muscle.

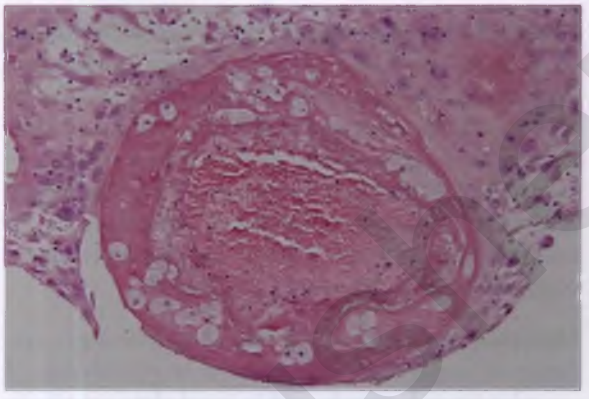

Figure 5.3 Acute atherosis (fibrinoid necrosis plus foam cells) in a basal plate artery: cross-section of a spiral artery shows numerous vacuolated lipid-laden macrophages embedded in a background of glassy, deep-red fibrinoid necrosis with loss of vascular endothelium.

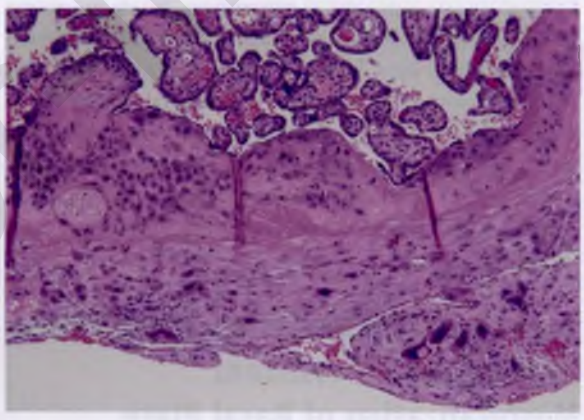

Figure 5.4 Increased placental-site giant cells: decidua basalis contains numerous multinucleated trophoblastic placental-site giant cells beneath Nitabuch's layer.

have stenotic lumens, and often show intramural foamy lipid-laden macrophages ("acute atherosis") (Figure 5.3). This distinction is particularly important because fibrinoid necrosis actually implies persistent muscularization, as it only occurs in arteries that retain their smooth muscle wall. A second feature of superficial implantation is increased placental site giant cells. Mature EVT normally exit the trophoblast cell columns by a form of epithelial mesenchymal transformation (EMT) to form isolated invasive cells that infiltrate the myometrium[9]. Once invasive EVT penetrate to the inner third of the myometrium, they undergo terminal differentiation to form placental-site giant cells. The presence of significant numbers of placental-site giant cells more superficially in the decidua indicates truncation of the normal invasive process and is another sign of superficial implantation (Figure 5.4)[10].

Ancillary Diagnostic Testing: There are no clinically useful ancillary techniques to make a diagnosis of superficial implantation. Although abnormal expression of HIF-1/TGF-beta 3, STOX11/CTNNA, HB-EGF/HER1, Nodal/Activin 7 receptor, and LAIR1/

LAIR2 have all been implicated in superficial invasion, none has been exploited for diagnostic purposes [11–15].

Prognostic Implications: Superficial implantation is associated with subsequent maternal vascular malperfusion. The prognostic significance of the latter is covered in more detail in Chapter 7. Affected mothers are at increased risk for later cardiovascular disease and recurrence in subsequent pregnancies[16]. The fetus is at risk for growth restriction, preterm delivery, and fetal death[17–19]. Long-term risks for the fetus following delivery include short stature, obesity, cardiovascular disease, and neurodisability[20,21].

Knowledge Gaps: We lack a clear mechanistic understanding of the molecular circuitry involved in abnormal trophoblast function and interaction with maternal tissues. Preeclampsia has been separated into two broad subgroups: cases occurring with relatively normal placentas in first pregnancies and cases associated with superficial implantation that more commonly recur in subsequent pregnancies[22]. Better tools for classification could lead to progress in treating the index pregnancy, managing future pregnancies, and predicting the risk of future cardiovascular disease in both the mother and child.

Excessive Immature (Transitional) Extravillous Trophoblast (Trophoblast Islands, Chorionic Cysts, Membranous / Basal Plate Microcysts, Increased Immature Intermediate Trophoblast)

Definition: Aggregation of excessive numbers of incompletely differentiated, phenotypically immature ("transitional") extravillous trophoblast (EVT), sometimes with central cystic degeneration. Specific lesions can be separated by site as follows: intraplacental-type immature (transitional) EVT = trophoblast islands and chorionic cysts; membranous-type immature (transitional) EVT = chorionic microcysts; and basal plate-type immature (transitional) EVT = basal plate microcysts and large superficial aggregates of basal plate-type immature (transitional) EVT.

Clinical Context: Excessive immature (transitional) EVT tends to be more common in placentas from patients with preeclampsia and FGR, and can be an indicator of subtle or early maternal trophoblastic dysfunction. However, other placentas can show these features, generally in lesser amounts.

Proposed Pathogenesis: Normal pathways of trophoblast differentiation were delineated by immunohistochemistry in two seminal papers[23,24]. Primary or acquired defects in the extravillous pathway can lead to excessive immature (transitional) EVT at several sites. The mechanism has been most thoroughly studied in the basal plate where EVT arising from anchoring villi in the basal plate normally form cell columns with a gradient of increasing maturation, culminating in the emergence of fully mature invasive EVT[25]. Incomplete maturation in preeclampsia, possibly due to early hypoxia, is associated with a failure to upregulate alpha 1 integrin cell surface proteins which are required for successful tissue invasion. This results in the accumulation of basal plate-type immature (transitional) EVT near the anchoring villi and a paucity of deeper mature invasive EVT[26,27]. Aggregates of immature (transitional) EVT at all placental sites often undergo central degeneration, forming pseudocysts, usually referred to as "chorionic cysts." Fluid from these cysts has been shown to be rich in major basic protein, a protein of unknown function also expressed in eosinophils[28].

Gross Features: Matrix-type fibrinoid secreted by immature (transitional) EVT can occasionally lead to thickening of the basal plate or firm lesions in the parenchyma, which must be distinguished from maternal floor infarction (see Chapter 17). Large cysts within villous tissue (septal cysts) can mimic intervillous thrombi or mesenchymal dysplasia (see Chapters 9 and 11) (Figure 5.5). Cysts immediately below the chorionic plate can occasionally protrude into the amniotic cavity as large exophytic lesions (Figure 5.6). Decreased placental weight, elevated fetoplacental weight ratio, and villous infarction accompany these findings in some cases.

Microscopic Features: Excessive immature (transitional) EVT manifest histologically as cohesive aggregates of small- to intermediate-sized cuboidal cells with a moderate amount of either eosinophilic or vacuolated cytoplasm. Trophoblast islands are aggregates of intraplacental-type immature (transitional) EVT within the parenchyma, often abutting large stem villi (Figure 5.7). They are generally associated with large amounts of extracellular matrix-type fibrinoid. Rarely, EVT within these islands can show

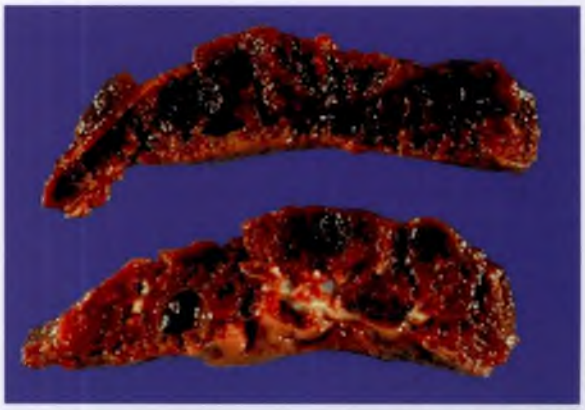

Figure 5.5 Chorionic cyst, intraplacental: smooth-walled cyst (lower left) containing traces of clear fluid.

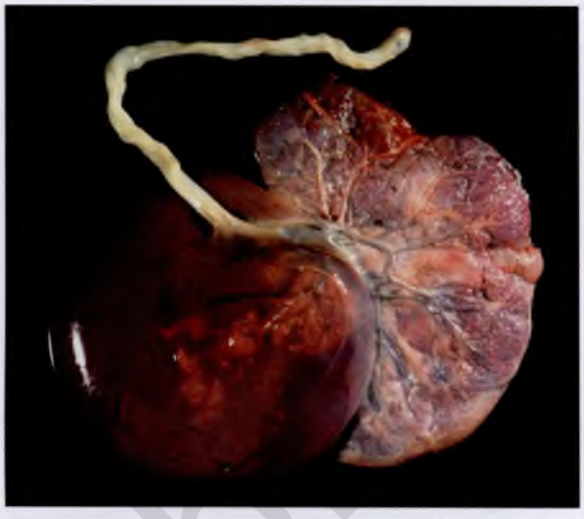

Figure 5.6 Chorionic cyst, exophytic, chorionic plate: large, thin-walled cyst with its base near the umbilical insertion site herniates through the chorionic plate.

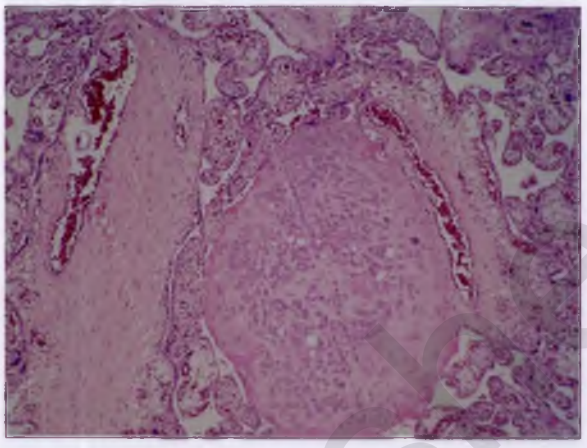

Figure 5.7 Trophoblast islands, intraplacental: loose aggregates of intraplacental-type immature (transitional) extravillous trophoblast are embedded in extracellular matrix-type fibrinoid.

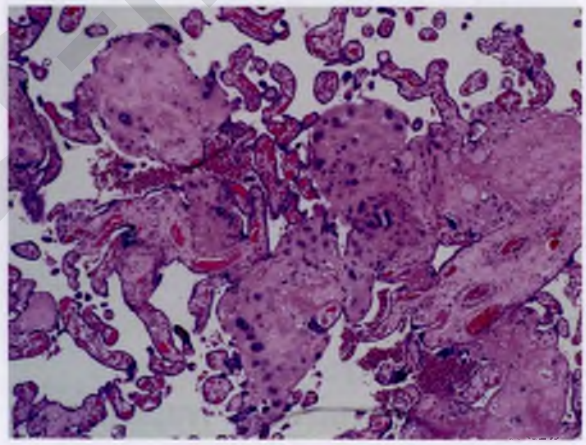

Figure 5.8 Nuclear atypia, intraplacental-type immature (transitional) extravillous trophoblast: individual trophoblast show significant nuclear enlargement and hyperchromasia ("degenerative-type atypia").

marked nuclear enlargement and atypia of the senescent type seen in bizarre leiomyomas (Figure 5.8). This finding is of no clinical significance, but must be distinguished from intraplacental choriocarcinoma, which is discussed in Chapter 4. Trophoblast islands often undergo cystic degeneration to form intraplacental chorionic cysts (Figure 5.9). The finding of more than 5 trophoblast islands or chorionic cysts per microscopic slide has been proposed as a threshold for abnormality[29]. Chorionic microcysts are small cysts, usually 0.2–1 mm, arising in a thickened layer (more than 7 cells) of membranous-type immature (transitional) EVT within the chorion laevae of the placental membranes (Figure 5.10)[30]. More than 3 microcysts per membrane roll has been proposed as a threshold of abnormality. Excessive basal plate-type immature (transitional) EVT with microcysts is seen in some placentas with superficial implantation. None of the above findings are by themselves alone diagnostic of a maternal vascular/trophoblastic disorder. Rather, when seen together or with the other more specific findings in this and the

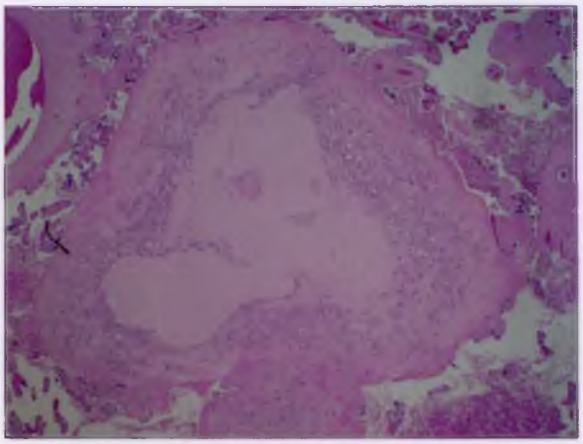

Figure 5.9 Chorionic (septal) cyst, intraplacental: large trophoblast island with central cystic degeneration (pseudocyst-formation) containing pink-staining, non-hemorrhagic fluid.

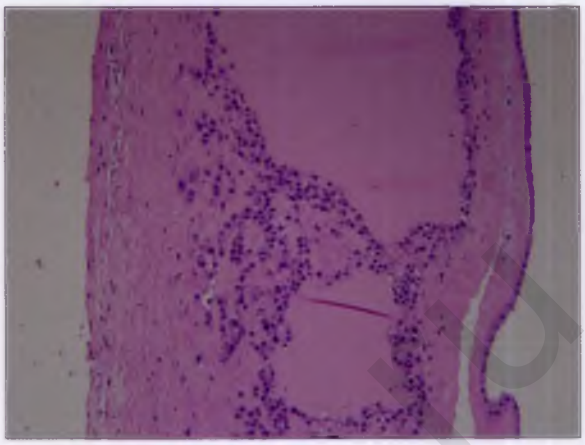

Figure 5.10 Membrane microcysts: trophoblast, focally vacuolated, within the chorion laevae of placental membranes shows cystic degeneration similar to Figure 5.9.

following three chapters, they provide additional support for such a diagnosis.

Ancillary Diagnostic Testing: Immature (transitional) EVTs have the following immunophenotype: p63 positive, Ki-67 intermediate, Inhibin and MelCAM weak-variable[31]. With the exception of a single abstract, this immunoprofile has not been exploited for diagnostic purposes[32].

Prognostic Implications: Excessive immature (transitional) EVT has not been associated with clinical outcomes independent of accompanying changes of maternal vascular malperfusion

Knowledge Gaps: Unique biomarkers for immature (transitional) EVT are not available. If such biomarkers were secreted into the circulation, or shed within exosomes, antenatal diagnosis might be feasible.

Decidual arteriopathy (Mural Hypertrophy, Hypertrophic Arteriopathy, Chronic Perivasculitis, Acute Atherosis, Fibrinoid Necrosis, Intramural Lipid-Laden Macrophages/ Foam Cells,)

Definition: Pathologic alterations including muscular hypertrophy, endothelial/vascular smooth muscle degeneration, fibrinoid necrosis, mural infiltration by lipid-laden macrophages (foam cells), and perivascular chronic inflammation affecting small- to medium-sized arteries and arterioles. All of these changes are best seen within arterioles in the marginal decidua at the junction of the placental disc and membranes.

Clinical Context: The prevalence of decidual arteriopathy is highest in preeclampsia accompanied by FGR and/or abnormal pulsed flow Doppler testing (50–60 percent of cases)[33]. It is also commonly observed in preeclampsia without FGR, well-controlled chronic hypertension, gestational and pregestational diabetes mellitus, and connective tissue diseases, including the antiphospholipid syndrome (15–25 percent of cases)[34–36]. It is not usually seen in FGR with normal pulsed flow Doppler testing or other clinical conditions associated with adverse outcomes. The number of affected vessels has been correlated with increased severity and decreased gestational age in preeclampsia[37].

Proposed Pathogenesis: Mural hypertrophy has been associated with alterations of the renin-angiotensin system and specifically with the angiotensinogen T235 allele that predisposes to chronic hypertension [4]. Acute atherosis, its immediate precursor (hypertrophic decidual arteriopathy), and its component parts (fibrinoid necrosis and foam cells), have been shown ultra-structurally to represent a sequence characterized by endothelial damage with insudation of plasma, lipid accumulation, and myointimal proliferation followed by ingress of macrophages that

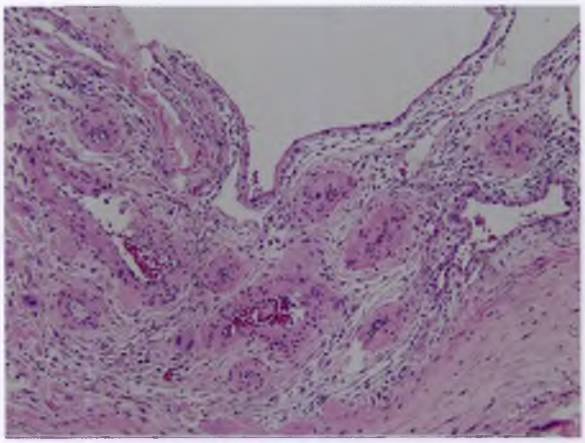

Figure 5.11 Decidual arteriopathy, mural hypertrophy, arterioles at the placental margin: vascular smooth muscle hypertrophy narrowing the vascular lumen to 1/3 or less of the total diameter.

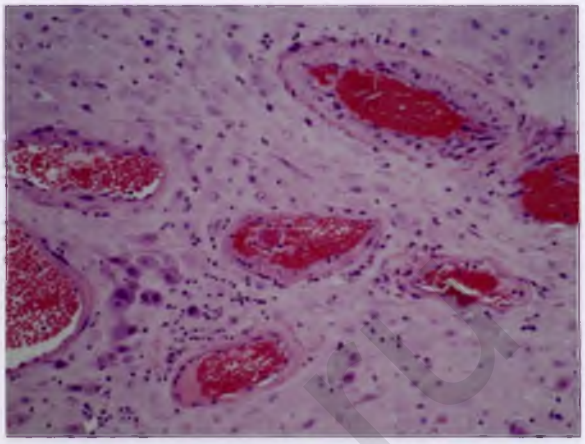

Figure 5.12 Decidual arteriopathy, hypertrophic type with chronic perivasculitis: arterioles at the placental margin: vessels show prominent muscular hypertrophy and early degenerative changes accompanied by a surrounding nonspecific chronic mononuclear cell infiltrate.

phagocytose the extracellular lipid[38]. In severe cases, atherosis can lead to massive mural intravasation of fibrin, luminal thrombosis, and/or vessel rupture. Studies over the past 15 years have implicated circulating antiangiogenic factors, such as soluble-VEGF receptor 1 (s-flt-1) and soluble endoglin (sENG), as primary endotheliotoxic agents[39,40]. Circulating anti-endothelial antibodies (e.g. antiphospholipid antibody) may exert a similar effect. Recent studies suggest that impaired endothelial nitric oxide synthase function may represent a final common pathway of injury, and that sildenafil or pravastatin may be therapeutic[41,42].

Gross Features: Placentas with decidual arteriopathy are often, but not always associated with decreased placental weight, and increased fetoplacental weight ratio (see Chapter 16). Acute atherosis affecting basal plate vessels can lead to villous infarction or rupture and abruptio placentae (see Chapters 7 and 8). Mural hypertrophy in association with diabetes, chronic hypertension, and some cases of preeclampsia at term can paradoxically be associated with increased placental weight (placentomegaly).

Microscopic Features: While most frequently involving arterioles in the marginal decidua of the membrane roll, arteriopathy can affect any muscularized artery in the vicinity of the gravid uterus[43,44]. Remodeled arteries in the basal plate and superficial myometrium (i.e. those with "physiologic change") are not susceptible, but basal plate arteries with "persistent muscularization" may be affected as described in the previous section. A few centers utilize placental bed biopsies after delivery of the placenta to look for arteriopathy in deep uterine vessels. A recent review summarizes pathologic changes in these biopsies[45]. The term mural hypertrophy applies only to marginal arterioles and is defined by concentric thickening of the vessel wall (lumen occupies less than 30 percent of diameter) due to a combination of medial and/or myointimal hyperplasia, hypertrophy, and extracellular matrix deposition (Figure 5.11). This lesion rarely progresses with chronic hypertension or diabetes alone. With superimposed preeclampsia, antiphospholipid antibodies, or abnormal pulsed flow Doppler testing, early degenerative changes lead to a transitional lesion termed "hypertrophic arteriopathy." A recent study of this lesion demonstrated enlargement and detachment of endothelial cells, and fragmentation and loss of myocytes (Figure 5.12)[46]. In many cases, there is also an associated chronic perivascular mononuclear cell infiltrate, and some vessels may show early focal fibrinoid necrosis. Hypertrophic arteriopathy can in turn progress to the final stage of decidual arteriopathy – acute atherosis, which is defined by fibrinoid necrosis (red-blue glassy degeneration of the arterial smooth muscle cells) and intramural lipid-laden macrophages (foam cells) (Figure 5.13). Either of the latter findings can

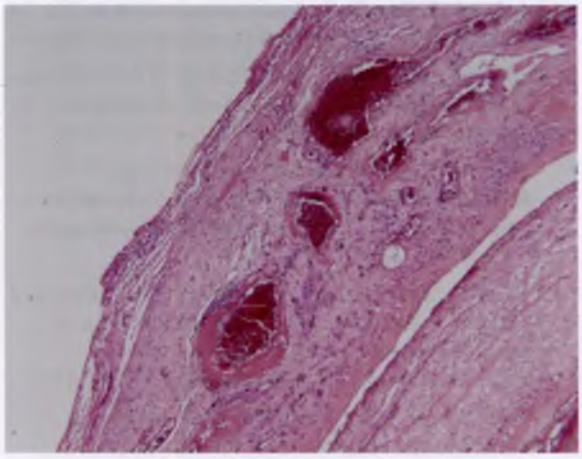

Figure 5.13 Decidual arteriopathy, acute atherosis (fibrinoid necrosis and foam cells): smaller arterioles at the placental margin show the same histologic changes described in Figure 5.3.

also be diagnosed separately, but caution is recomm ended to avoid overdiagnosis[47].

Ancillary Diagnostic Testing: Immunohistochemical staining for CD31, desmin, and CD45RO can help document hypertrophic arteriopathy with chronic perivasculitis, but is not usually necessary[46].

Prognostic Implications: Acute atherosis is associated with an elevated long-term risk for abnormal cardiovascular function that is not seen in preeclamptic mothers lacking this histologic finding[48]. Atherosis, in common with other severe maternal vascular/ trophoblastic placental lesions, has a high recurrence risk, especially when associated with FGR and prematurity (see Chapters 31 and 32).

Knowledge Gaps: Whether circulating factors associated with acute atherosis in the placenta cause similar histologic lesions in distant maternal vessels is not known. Why some patients with preeclampsia lack arteriopathy remains poorly understood.

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Chapter 6

Distal Villous Hypoplasia, Focal and Diffuse

Brendan Fitzgerald and Sarah Keating

Distal Villous Hypoplasia (Diffuse Villous Paucity, Terminal Villous Deficiency)

Definition: Distal villous hypoplasia is a villous developmental abnormality characterized by the presence of reduced numbers of terminal villi with resultant prominence of the intervillous space. The villi in distal villous hypoplasia have reduced branching and so typically appear elongated and thin, and in severe cases often show reduced vascularity with increased stromal density and thinning of their covering villous trophoblast layers[1]. Distal villous hypoplasia may be a diffuse and dominant finding in some placentas or it may be a focal abnormality, typically in placentas that show other lesions associated with maternal vascular malperfusion.

Clinical Context: The classical clinical association is with early onset intrauterine growth restriction associated with reduced or absent end diastolic flow on umbilical artery Doppler[2,3,4]. As there is frequent clinical overlap between growth restriction and pregnancy-induced hypertensive disorders, distal villous hypoplasia may also be seen to varying degrees in pregnancies with pregnancy-induced hypertension or preeclampsia. For this reason, distal villous hypoplasia and pathological lesions associated with maternal vascular malperfusion often coexist to varying degrees. On antenatal sonographic evaluation of placental morphology, abnormally small but thick placentas have been linked to poor pregnancy outcomes (also see Chapter 16)[5,6]. In some instances, such placentas have shown distal villous hypoplasia[7]. Distal villous hypoplasia has also been demonstrated in some pregnancies showing abnormalities of maternal serum β-HCG and inhibin[8], which are components of maternal screening programs for fetal anomalies. Indeed, abnormalities in some analytes used in screening programs can lead to false positive screen results and ultimate referral for investigation for placental dysfunction[9]. Because of its association with growth restriction and preeclampsia, distal villous hypoplasia may be associated with prematurity, miscarriage and stillbirth.

Proposed Pathogenesis: As with many abnormalities of placental development, the etiology of distal villous hypoplasia is incompletely understood. Villous growth is dependent on coordinated trophoblast proliferation and angiogenesis, with the early events in implantation having a critical influence. In the first trimester, material arterioles at the site of the future definitive placental disc become plugged by extravillous trophoblast so that the placenta develops in a relatively hypoxic environment. The absence of such plugging outside of the implantation site, in areas that will ultimately form the placental membranes, leads to oxidative stress and regression of the villous tree (chorion regression)[10]. In some circumstances, defective trophoblast invasion of the placenta bed may lead to impaired plugging of these arterioles and early exposure of areas of the developing placenta to higher than normal oxygen tensions, leading to impaired villous development[10]. Such regression is in part mediated by an effect on angiogenesis, and dysregulation of angiogenesis may also act at later times in pregnancy to cause impaired villous growth. Some angiogenic factors, such as placental growth factor, are among the many serum analytes now being investigated as being potentially predictive of pregnancy complications, including fetal growth restriction[11]. An increased frequency of distal villous hypoplasia has been observed in placentas from pregnancies in which there were elevated second trimester screening markers Inhibin-A and β-hCG. As both of these are produced by syncytiotrophoblast, the elevations are proposed to be due to abnormalities in villous trophoblast turnover that ultimately led to trophoblast depletion and impaired villous growth[8]. A variety of etiological mechanisms have been proposed, and until it is better understood, it may be

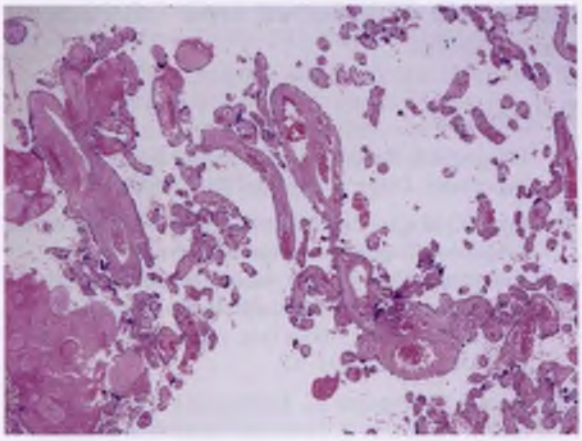

Figure 6.1 Distal villous hypoplasia showing reduced numbers of terminal villi with stem villi appearing closer together than normal.

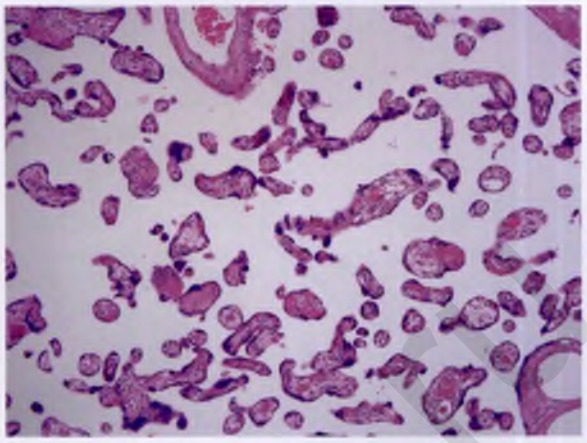

Figure 6.2 Distal villous hypoplasia at 32 weeks gestation. Terminal villi are widely spaced and small for gestational age with an increase in syncytial knots.

most appropriate to consider distal villous hypoplasia to be an abnormal villous developmental phenotype that may potentially be the endpoint of a number of different pathological processes.

Gross Features: The placenta may be small in size and weight, and may show evidence of excess chorion regression with marginal cord insertion (also see Chapter 16). On sectioning of the disc, the placental texture can be unremarkable, but occasionally it may appear loose. Because of its association with maternal vascular malperfusion, lesions such as infarction and fibrin(oid) deposition may be present.

Microscopic Features: As villous development varies through the placentome (placental lobule), evaluation for the presence of distal villous hypoplasia needs to be performed in regions where villous development is normally at its most complete. Areas where terminal villous development is normally sparse should be avoided, such as the area beneath the chorionic plate as well as the central placentome. If villous development appears sparse continuously or multifocally as a slide is scanned from side to side across its lower two-thirds, then this is abnormal. In the Amsterdam Placental Workshop Guidelines, distal villous hypoplasia is diagnosed if there is involvement of ≥ 30 percent of a full thickness section; focal distal villous hypoplasia is defined as involvement of one section only; a diagnosis of diffuse distal villous hypoplasia requires involvement of two or more slides[12]. Often, diffuse involvement is associated with a reduction in placental weight. On low-power examination, widening of the intervillous space is also often the most noticeable abnormality, and on low power there is a reduction in the numbers of terminal villi compared to stem villi so that the stem villi appear closer together (Figures 6.1 and 6.2). On higher-power examination, the villi appear small and elongated with reduced branching. Vascularity is variable but is often reduced with an accompanying increase in stromal density. Nuclei within the villous trophoblast may appear to show increased nuclear density and to form more prominent syncytial knots than usual; at the same time total villous trophoblast thickness may appear reduced. The extent of syncytial knotting is variable but in some cases it may be prominent. A distinct form of syncytial knotting may be prominent in placentas showing distal villous hypoplasia referred to as "wave-like" syncytial knotting (Figure 6.3)[8,13]. These are most easily identified along the edges of non-branched villi, where they appear as a repeating pattern of small knots with very condensed dark nuclei.

Ancillary Diagnostic Testing: This is generally not required. Immunohistochemistry for cytokeratins may highlight thinning and depletion of villous trophoblast. Although fetal growth restriction may be associated with abnormal placental genetics (confined placental mosaicism) and some maternal conditions, there is currently no recommendation for further diagnostic testing based on the presence of distal villous hypoplasia alone.

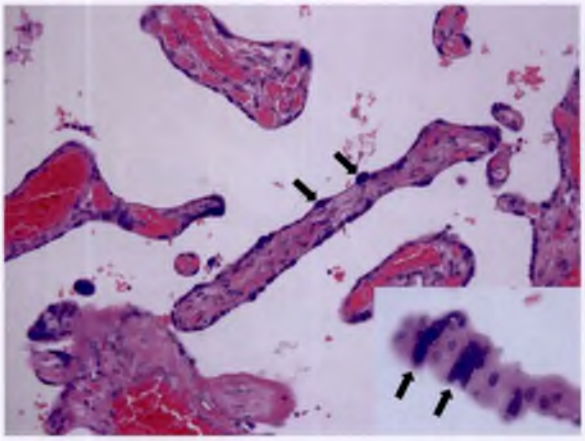

Figure 6.3 Abnormal long, non-branching villus in distal villous hypoplasia at 34 weeks gestation. "Wave-like" syncytial knots are evident as repeating bulges along the surface of the villus in an otherwise thinned trophoblast layer. The inset shows the rings of nuclei within the syncytium that result in "wave-like" knot formation.

Prognostic Implications: The impact of distal villous hypoplasia on a pregnancy depends on many factors. If it is a diffuse histologic finding and associated with small placental size, the fetus may be growth-restricted, and premature delivery may be indicated to protect fetal well-being and avoid pregnancy loss. With focal distal villous hypoplasia, the effect may depend on the presence of other lesions, e.g. infarction or other clinical effects of maternal vascular malperfusion. It is increasingly apparent that in utero growth restriction may have consequences for adult health[14], although direct links between specific pathologies and adult outcomes are lacking.

Knowledge Gaps: A variety of etiological mechanisms have been proposed for placental maldevelopment, and it is possible that the lesion that we interpret as distal villous hypoplasia may represent a phenotype that is the consequence or endpoint of a number of pathological processes. Although knowledge of the molecular basis of placental function and dysfunction is increasing rapidly, there is still no complete understanding of the pathological processes that lead to villous maldevelopment. Such an understanding may ultimately lead to interventions that encourage villous growth. Recently the presence of distal villous hypoplasia has been shown to correlate with a lower fractal dimension[15]. With increasing use of digital pathology, it may be that in time, image analysis will assist pathologists in obtaining objective measures of villous volumes and shape that will assist with diagnostic reproducibility.

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Chapter 7

Maternal Vascular Malperfusion

Raymond W. Redline

Maternal vascular malperfusion can be separated into two distinct categories: global/partial (accelerated villous maturation) and segmental/complete (infarction and infarction hematoma/rounded intraplacental hematoma)[1]. While primarily a consequence of trophoblast dysfunction and insufficient arterial remodeling, as described in Chapter 5, other factors such as increased vascular tone in uterine arteries proximal to the maximum extent of trophoblast invasion, failure to increase circulating blood volume during pregnancy, and placental implantation in a region with poor arterial supply may contribute. Recent work has shown that the previous view that uniform underperfusion of the intervillous space directly causes hypoxia is overly simplistic[2]. The term malperfusion accommodates more recent concepts such as intermittent interruptions of flow, increased velocity of flow creating maternal-fetal perfusion mismatch, and intervillous hyperoxia developing secondary to decreased placental function.

Accelerated Villous Maturation (Global / Partial Maternal Vascular Malperfusion, Increased Syncytial Knots [Syncytial Nuclear Aggregates], Increased Intervillous Fibrin, Villous Agglutination, Villous Paucity, Microinfarcts, Tenney-Parker Change)

Definition: Accelerated villous maturation (AVM) is an umbrella term describing a complex of microscopic findings in the lower two-thirds of the placental parenchyma, including regions of villous undergrowth and paucity alternating with regions of villous crowding showing focally increased syncytial knots, intervillous fibrin deposition, and villous agglutination[3]. The term AVM alludes to the similarity with changes seen in the progression from preterm to term/postterm villous histology.

Clinical context: The full spectrum of maternal vascular malperfusion, including AVM, is most commonly seen with fetal growth restriction (FGR) associated with preeclampsia, longstanding pregestational diabetes, autoimmune disease, confined placental mosaicism, and abnormal pulsed flow Doppler testing[4–8]. Lesser degrees of AVM may be seen in the absence of FGR with obesity, gestational diabetes, sleep-disordered breathing, pregnancy at high altitudes, thrombophilia, and some cases of spontaneous preterm birth, particularly when associated with premature rupture of membranes[9–14].

Proposed Pathogenesis: Irregular and variable narrowing of the uterine arteries due to defective remodeling and decidual arteriopathy results in maternal blood entering the placental cotyledons unevenly and at high velocity[2]. Preferential distribution of the initial arterial jets to poorly gas exchanging proximal villi in the upper one-third of the placenta and rapid egress due to abnormal cotyledonary architecture eventually culminate in reduced oxygen uptake, increased intervilllous oxygen tension, and oxidative stress. The resultant combination of stasis, ischemia, sheer stress, apoptosis, and focal tissue necrosis leads to an increased rate of formation relative to clearance of syncytial knots, villous agglutination and fibrin deposition, and areas of reduced villous growth (paucity)[15]. Increased fibrin is a combination of fibrin-type fibrinoid related to circulatory stasis and matrix-type fibrinoid secreted by intraplacental-type immature (transitional) extravillous trophoblast (see Chapter 5)[16].

Gross Features: Placentas with AVM are generally small for gestational age with an increased fetoplacental weight ratio. Pathologists should carefully consider whether to make a diagnosis of AVM without some reduction in fetal or placental weight. Macroscopic lesions such as thin umbilical cord (<8 mm maximum diameter), villous infarcts, and perivillous fibrin plaques are commonly associated with AVM[3]. Some

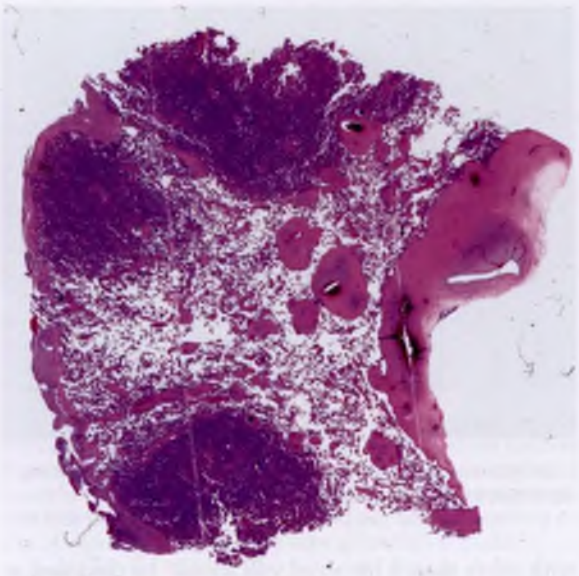

Figure 7.1 Accelerated villous maturation (global/partial maternal vascular malperfusion). Whole slide image shows alternating areas of villous paucity and crowding.

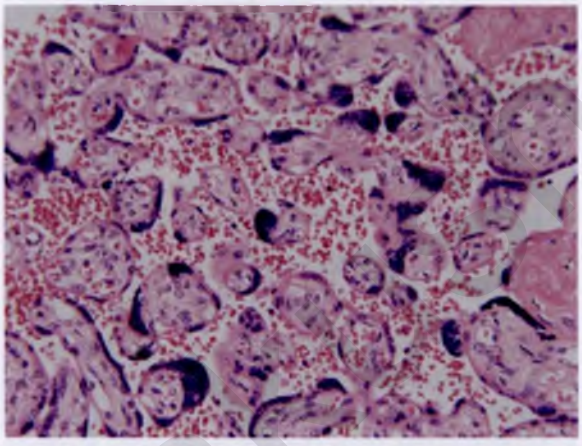

Figure 7.3 Increased syncytial knots, distal villi. Clusters of syncytiotrophoblast nuclei are aggregated at the margins of most villi.

authors have found an association with decreased placental diameter (chorion regression), increased placental thickness, placental elongation (increased length minus breadth), and peripheral umbilical cord insertion (see Chapter 16).

Microscopic Features: The most reliable histologic indicator of AVM is an alternating low-power pattern of villous crowding and paucity (Figure 7.1). This

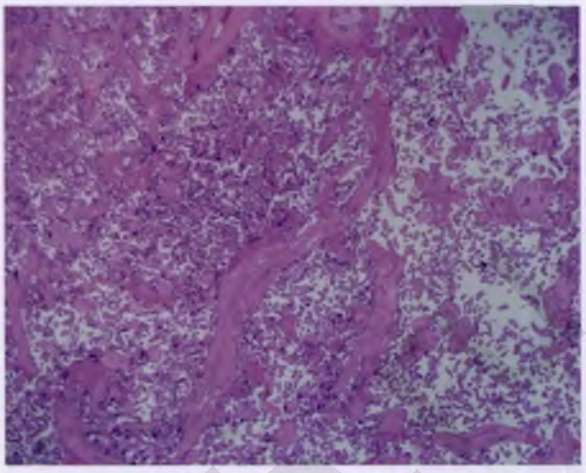

Figure 7.2 Accelerated villous maturation (global/partial maternal vascular malperfusion). Low-power image shows distal villous agglutination with increased syncytial knots in the vicinity of stem villi on the left and scant thin, poorly branching distal villi on the right.

subjective impression of increased variation in villus packing density has recently been verified by image analysis in placentas with increased fetoplacental ratios[17]. Examination of the crowded areas at higher magnification reveals increased syncytial knots, accumulation of intervillous fibrin, and foci of villous agglutination (Figure 7.2). Syncytial knots (also known as "syncytial nuclear aggregates") are defined as aggregates of > 5 clustered syncytiotrophoblast nuclei with hyperchromatic heterochromatin projecting into the intervillous space from the surface of distal villi (Figure 7.3). This terminology (syncytial knots/nuclear aggregates) is meant to encompass syncytial bridges, and so-called sectioning artifacts, but not syncytial sprouts, whose nuclei have dispersed euchromatin and nucleoli (see Chapter 1). Normal term and postterm placentas also have numerous syncytial knots, but these are more diffusely distributed and lack the areas of villous paucity seen with AVM. A threshold of more than 30–33 percent of villi showing syncytial knots after counting of at least 100 villi in the lower two-thirds of the placenta has been suggested[18]. Unfortunately, the AVM pattern is not uniform, making reproducibility a challenge. Increased intervillous fibrin is characterized by irregular aggregates of both fibrin-type and matrix-type fibrinoid eccentrically projecting from proximal and distal villi (Figure 7.4). This feature also accounts for so-called fibrinoid necrosis of villi, which simply

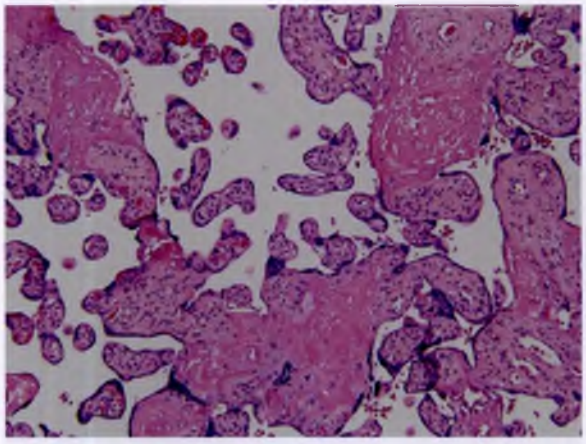

Figure 7.4 Increased intervillous fibrin, intervillous space. Amorphous aggregates of fibrin-type fibrinoid adhere to portions of the villous surface without completely surrounding them.

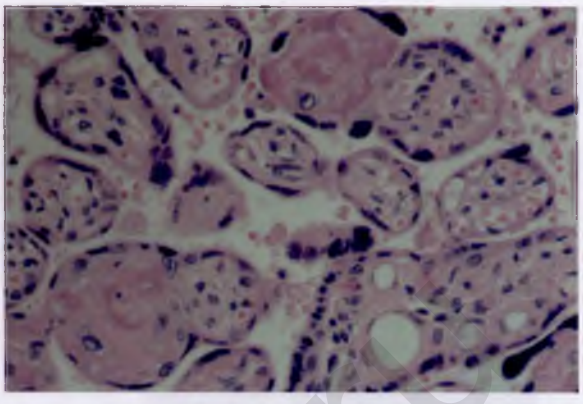

Figure 7.5 Increased intervillous fibrin, intravillous (so-called fibrinoid necrosis of villi). Nodular aggregates of fibrin-type fibrinoid have been incorporated into the villous stroma by a layer of reparative syncytiotrophoblast.

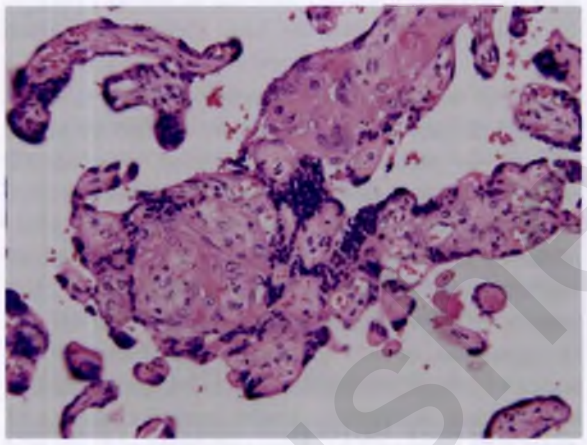

Figure 7.6 Villous agglutination ("microinfarcts"), distal villi. Groups of adherent, partially fibrotic distal villi are intermixed with intraplacental extravillous trophoblasts and matrix-type fibrinoids.

represents re-epithelialized nodules of intervillous fibrin incorporated into the villous stroma (Figure 7.5)[19]. Increased intervillous fibrin is distinguished from trophoblast cell islands (see Chapter 5) by its more diffuse nature and from massive perivillous fibrin deposition (see Chapter 17) in that it does not completely surround distal villi. Villous agglutination is defined by small clusters of distal villi with degenerative changes including fibrosis, partial loss of villous capillaries, and an attenuated trophoblastic layer with fibrin and necrotic cell fragments (also known as "microinfarcts") (Figure 7.6). Similar areas with more than 5 involved villi should be classified as true villous infarcts (see next section). Finally, villous paucity refers to areas with decreased numbers of thin, poorly branching villi (Figure 7.1 and 7.2). If the areas with paucity exceed 30 percent of the villous parenchyma in the lower two-thirds of a full thickness block, a diagnosis of distal villous hypoplasia should be made (see Chapter 6).

Ancillary Diagnostic Testing: There are no clinically useful ancillary techniques to make a pathologic diagnosis of maternal vascular malperfusion. Methods for quantitating severity in routine H&E sections include a scoring system that awards points for each of its components (individual features of accelerated maturation, placental hypoplasia, decidual arteriopathy, excessive placental-site giant cells, trophoblast islands, and villous infarcts) and use of a grid for quantitation of syncytial knots[10][20]. Reduced maternal plasma angiogenic index (PlGF/sflt-1 ratio), a measure of maternal endothelial damage, at 20–23 weeks has recently been validated as a biomarker for changes consistent with maternal vascular malperfusion in delivered placentas at all gestational ages[21].

Prognostic Implications: Mothers with AVM are at increased risk for later cardiovascular disease and recurrence in subsequent pregnancies. Fetuses are at risk for FGR, preterm delivery, and intrauterine fetal death (IUFD)[22–24]. Adverse effects in the preterm neonate may be reduced in the short term, but the risk of later chronic lung disease is increased[25][26]. Other long-term risks include short stature, obesity, cardiovascular disease, and neurodisability[27–29].

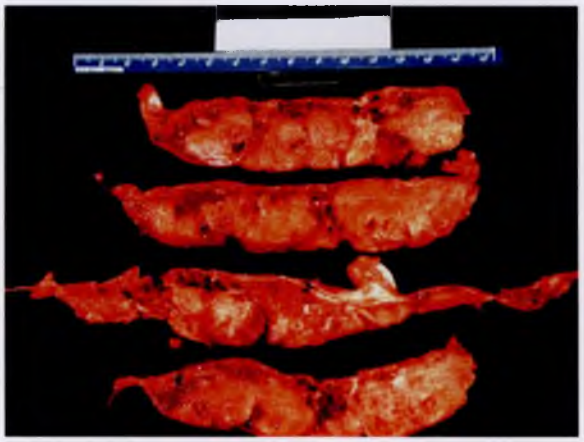

Figure 7.7 Multiple villous infarcts. Cut surface of the placental parenchyma shows multiple wedge-shaped pale firm granular areas with their broad edge abutting the basal plate, each representing an area of villous infarction resulting from spiral artery occlusion.

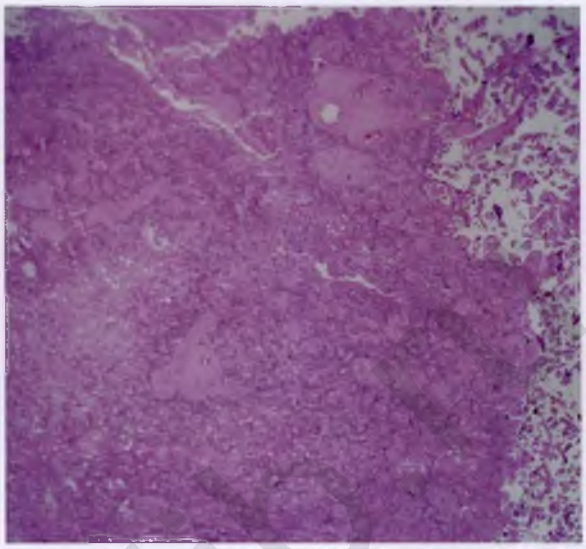

Figure 7.8 Villous infarct, low-power view. The lesion is well-circumscribed and characterized by large areas of degenerating villi in close contact due to collapse of the intervillous space.

Knowledge Gaps: Reconciliation of the qualitative histologic approach outlined above with other systems based on morphometry or pathophysiological concepts such as preuterine, uterine, and postuterine hypoxia is necessary[30]. Boundaries and distinctions between severe AVM and distal villous hypoplasia need to be clarified[1]. Additional correlation with imaging and serum biomarkers may lead to antenatal diagnosis and treatment.

Villous Infarcts, Remote and Recent (Segmental / Complete Maternal Vascular Malperfusion)

Definition: Basally oriented groups of more than 5 villi (usually many more) showing collapse of the intervillous space, scattered karyorrhectic debris and neutrophils between villi, ischemic necrosis and gradual dissolution of villous trophoblast, and degenerative villous stromal changes.

Clinical Context: Villous infarcts are most commonly seen in association with FGR associated with preeclampsia, longstanding pregestational diabetes, autoimmune disease, thrombophilia, confined placental mosaicism, and abnormal pulsed flow Doppler testing[4,7,8,31–33]. They are occasionally seen in normal term gestations and have an increased incidence in term pregnancies complicated by preeclampsia, stable chronic hypertension, obesity, gestational diabetes, smoking, and first pregnancy at older age[34].

Proposed Pathogenesis: Villous infarcts reflect sudden complete loss of maternal vascular perfusion secondary to either spiral artery thrombosis or premature separation of the placenta[35].

Gross Features: Villous infarcts are firm lesions, granular on cut section, with their broad base abutting the maternal surface (Figure 7.7). Early infarcts are red in color, older ones yellow. Increasing number, central location, and both maximum diameter and total percentage of parenchymal involvement are all adverse prognostic indicators. Perivillous fibrin plaques, intervillous thrombi, chorangiomas, atrophy, and massive perivillous fibrin deposition can all mimic villous infarcts and must be differentiated by histology. Decreased placental weight, elevated feto-placental weight ratio, thin umbilical cord, and abnormal placental shape are commonly associated findings (see Chapter 16).

Microscopic Features: Villous infarcts have a well-circumscribed margin and are contiguous with the basal plate on low magnification (Figure 7.8). Superficial implantation and spiral artery thrombi are occasionally seen underlying the infarct. Higher magnification reveals collapse of the intervillous space with agglutination of villi. Karyorrhectic debris, neutrophils, and traces of fibrin surround the collapsed villi. The villous trophoblast initially loses

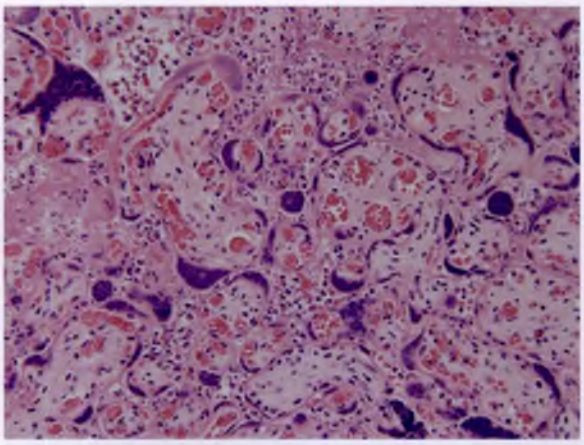

Figure 7.9 Recent villous infarct. Villi are agglutinated due to collapse of the intervillous space and show acute ischemic changes including focal loss of trophoblast basophilia, perivillous fibrin, and acute inflammatory cells.

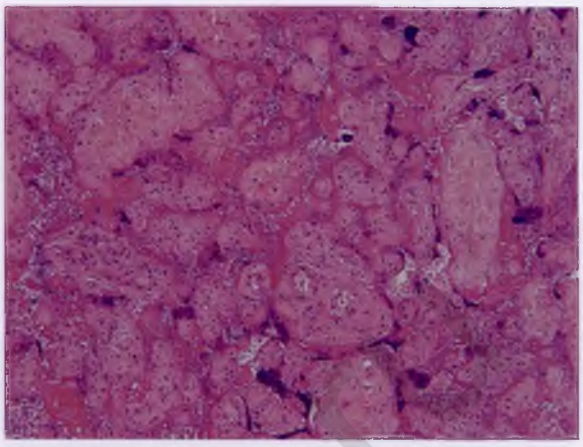

Figure 7.10 Remote villous infarct. Villi are in direct contact due to collapse of the intervillous space. Surrounding fibrin is condensed and diffuse with scant necrotic debris. Syncytiotrophoblast shows advanced degenerative changes. Villous stroma is fibrotic with loss of capillaries, but intermediate-sized vessels remain patent.

nuclear basophilia. The villous stroma at early stages retains its fetal vascular architecture with some mild degenerative changes (Figure 7.9). Large stem villous vessels may show luminal obliteration. Later infarcts develop stromal fibrosis and involution of trophoblast and fetal vessels (Figure 7.10). Remote infarcts are distinguished from perivillous fibrin plaques and massive perivillous fibrin deposition (see Chapter 17) by close contiguity of the villi (due to collapse of the intervillous space) and absence of matrix-type fibrinoid and intraplacental-type immature (transitional) extravillous trophoblast. Villous atrophy is a more diffuse process associated with decreased placental thickness, which shows histologic features that overlap with perivillous fibrin plaques (see Chapter 17). Chorangiomas and intervillous thrombi are immediately distinguished from infarcts by their typical histologic characteristics (see Chapters 9 and 11).

Ancillary Diagnostic Testing: None currently used.

Prognostic Implications: Villous infarcts are more strongly associated with underlying maternal thrombophilia than AVM and are risk factors for stillbirth, FGR, and fetal CNS injury[24,36,37].

Knowledge Gaps: Why some otherwise normal placentas have infarcts while other placentas with severe global/ partial maternal vascular malperfusion do not is poorly understood.

Infarction Hematoma / Rounded Intraplacental Hematoma (Centrally Hemorrhagic Villous Infarct, Intervillous Thrombus with Surrounding Villous Infarction)

Definition: Centrally organizing hematoma, spherical in shape, surrounded by a layer of infarcted placental villi, at least 5 villi in diameter[38][39].

Clinical Context: The clinical scenarios associated with this lesion are similar to those seen with classic villous infarcts: preeclampsia, FGR, and chronic hypertension. Infarction hematoma/rounded intraplacental hematoma may be more common with placental abruption and stillbirth.

Proposed Pathogenesis: The spherical nature of the hematoma, the symmetric distribution of surrounding villi, and the similarity in age of the hematoma and surrounding infarcted villi suggest that these lesions may form as a consequence of spiral artery thrombosis followed by reestablishment of blood flow (ischemia-reperfusion)[38]. An alternative suggestion is that they are fundamentally hemorrhages (rounded intraplacental hematomas) with secondary infarction, i.e. an intraplacental abruption (further discussed in Chapter 18). In this model, a vasculopathic decidual vessel ruptures into the intervillous space pushing the

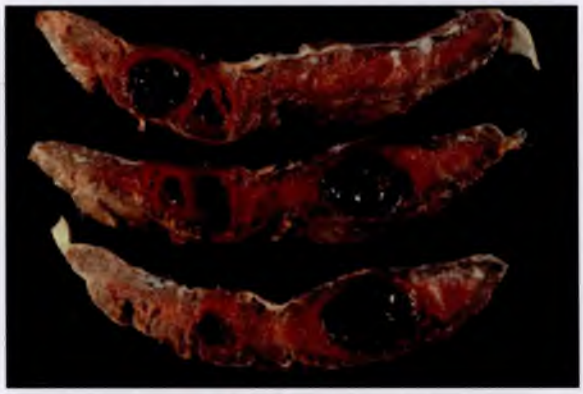

Figure 7.11 Multiple infarction hematomas (rounded intraplacental hematomas). Image provided by Robert Bendon, Kosair Children's Hospital, Louisville, KY. Cut surface of placental parenchyma shows several large, rounded hemorrhagic lesions surrounded by a mantle of pale, firm infarcted villi.

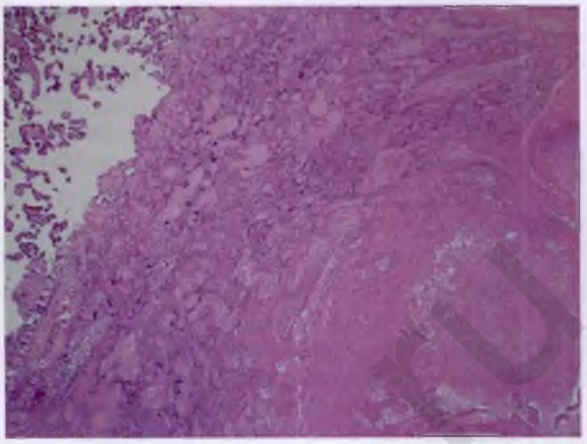

Figure 7.12 Infarction hematoma (rounded intraplacental hematoma). A loosely organized blood clot at the bottom right is surrounded by a mantle of remotely infarcted villi (greater than 5 villi in diameter). The lesion is well-circumscribed with unaffected villi in the upper left corner.

surrounding villi together, effectively walling off the lesion, and limiting its spread[39]. Having been cut off from its underlying blood supply, this rim of compressed tissue then undergoes infarction.

Gross Features: The appearance of infarction hematoma/rounded intraplacental hematoma varies by duration (old: yellow surrounding villi with brown central clot; recent: red, firm surrounding villi with dark red central clot), site of origin (more commonly central than marginal), and size (Figure 7.11). Lesions may be multiple and are often intermixed with classic villous infarcts in the same placenta.

Microscopic Features: The central hematoma in infarction hematoma/rounded intraplacental hematoma is generally spherical and may show signs of early organization (lines of Zahn). In remote lesions, the hematoma component shows signs of dissolution with loosely organized amorphous and flocculent pink debris. The surrounding infarcted villi show the same histologic characteristics as described for classic villous infarcts (Figure 7.12). Lesions with less than 5 layers of surrounding villi should be diagnosed as intervillous thrombi (see Chapter 11). Chorionic cysts with hemorrhagic cyst fluid may be superficially similar, but the central component is liquified and the surrounding solid component is composed of immature (transitional) extravillous trophoblast and matrix-type fibrinoid rather than infarcted villi (see Chapter 5).

Ancillary Diagnostic Testing: None currently used.

Prognostic Implications: A recent paper concentrating on cases with multiple infarction hematomas showed a strong association with stillbirth[38].

Knowledge Gaps: Further studies are needed to determine if infarction hematoma (infarction followed by reperfusion) or rounded intraplacental hematoma (spiral arterial rupture into the intervillous space) best represents the pathogenesis of this lesion. A population-based study of infarction hematomas including less severe examples might clarify possible associations with underlying hypertension, thrombophilia, and other clinical risk factors.

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Chapter 8

Loss of Maternal Vascular Integrity

Drucilla J. Roberts

The placenta is perfused by approximately 120 spiral arteries at term, delivering blood at 600–700cc/minute with a pressure of about 70 mmHg[1]. It is not surprising that breaches of this system can result in catastrophic maternal hemorrhage often referred to as abruption. Clinical placental abruption occurs in <1 percent of all deliveries but three to four times more are diagnosed pathologically[2,3]. There is a significant associated perinatal and maternal morbidity: placental abruption accounts for approximately one-third of perinatal deaths[4–6], and it is one of the most common causes of maternal disseminated intravascular coagulopathy (DIC)[7]. Breach of maternal vascular integrity is associated with a variety of pathologies and clinical scenarios. For example, acute chorioamnionitis is often associated with acute abruption[8] and hypertension with abruptions both acute and chronic[9]. Factors that result in loss of maternal vascular integrity include decidual necrosis from inflammation and/or infection mediated by cytokines[10], trauma (e.g. blunt force or uterine rupture), force/pressure from hypertension or increased venous pressure, and toxins (e.g. tobacco smoking and cocaine)[11]. This section will review three forms of placental abruption: classic acute abruptio placentae, acute marginal abruption, and chronic marginal abruption (sometimes associated with diffuse chorioamnionic hemosiderosis).

Acute Abruptio Placentae, Classic (Acute Abruption, Abruptio Placentae)

Definition: Premature separation of the placenta from the uterus by hemorrhage, usually arterial, after 20 weeks gestational age and before delivery of the fetus/infant.

Clinical Context: The incidence of acute abruptio placentae has been estimated to be in about 1 percent of all pregnancies[12]. Abruption can occur at any gestational age but is most common between 24 and 26 weeks[13]. Rates in the United States appear to be increasing, with the highest rates being present in African American women[14]. Women with acute abruptio placentae present differently depending on whether the abruption is apparent ("revealed") or silent ("concealed"). Apparent abruptions are more common but often will have a concealed component as well. Apparent acute abruptions present with bright-red blood loss per vaginam that can be painless or can be associated with abdominal pain due to uterine distension. Often there is fetal distress exemplified by bradycardia or fetal demise. Concealed abruptions present similarly, but do so without vaginal bleeding. Concealed abruptions often have severe uterine pain with a very firm uterus by palpation.

There may be associated maternal hyper- or hypotension contingent on the amount of blood loss in either case. Depending on the extent of the separation, there may be fetal compromise or death. Risk factors are many for acute abruption and include preterm premature rupture of the membranes (PPROM)[15,16], oligohydramnios[16], abnormal implantation[17], black race[14], tobacco smoking[18], hypertension[15], cocaine abuse[19], trauma[20–22], thyroid disease[23–25], male gender[26], implantation over leiomyomas,[27], antiphospholipid antibody syndrome[28], and acute chorioamnionitis[8]. There is a significant recurrence risk, and prior occurrence is the strongest risk factor for acute abruption in the index pregnancy[29]. There may also be a genetic predisposition[30–32]. Most acute abruptions will have one of these risk factors. Hypertension, whether pregnancy related or essential, accounts for approximately 35 percent of all acute abruptions.33 About 40 percent of acute abruptions are idiopathic[33–35].

Proposed Pathogenesis: Acute abruptio placentae is due to blood dissecting between the decidua basalis and the placenta. It is assumed to be arterial in etiology, with the higher pressure blood flow resulting in rapid, often massive, placental separation. Forces such as shearing (from trauma or rapid loss of fluid in cases

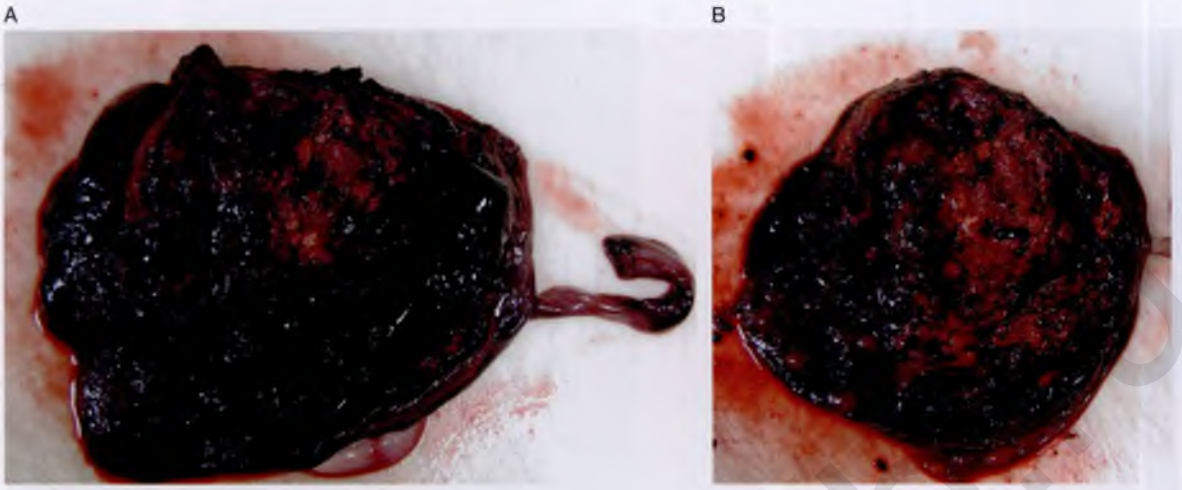

Figure 8.1 (a) Acute abruption with clot on the basal plate. (b) Same placenta with clot removed, revealing the residual "crater" of compressed villi (courtesy of B. Hargitai). Images provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

of polyhydramnios and ruptured membranes[12]) and pressure (from hypertension) have a clear pathogenesis. Other pathologies can predispose to abruption including decidual inflammation with resultant release of cytokines that cause decidual necrosis[10]. Abnormal, shallow implantation and decidual arteriopathy[17,36], both features of preeclampsia[37], are strong risk factors for acute abruptio placentae[38]. Familial cases[39] and recurrences[15] suggest a genetic component.[30,40]

Gross Features: Acute abruptio placentae often lacks a pathological footprint – i.e. no gross or histopathologic features. However, there are pathological features that can support and sometimes confirm the diagnosis of acute abruption. These include: loose and poorly organized retroplacental hemorrhage/hematoma, indentation and compression of the surrounding chorionic villi (Figure 8.1 and 8.2a), and intravillous hemorrhage (Figure 8.2b)[41]; see microscopic features below. Acute abruptio placentae is ideally diagnosed by gross examination of a fresh placenta immediately after delivery (therefore it is often a diagnosis made at delivery). Placentas evaluated remote from delivery can show container artifacts, making interpretation of placental indentation and retroplacental hemorrhage difficult.

Microscopic Features: Many histologic features have been described in association with acute abruption. These include dissecting hemorrhage in the decidua basalis, chorangiosis, intervillous hemorrhage, intravillous hemorrhage, trophoblastic smudging (early trophoblastic necrosis), and decidual inflammation[42,43]. Acute chorioamnionitis, especially preterm, carries a high risk for acute abruption[8,16,34], so the combination of chorioamnionitis and retroplacental or marginal hemorrhage (see section on acute marginal abruption) is a relatively frequent in premature deliveries. We sometimes use the term "inflammatory abruption" to describe these cases.

Prognostic Implications: Placental separation results in immediate interruption of maternal circulation to the placenta. Therefore, depending on the size of the separation, fetal compromise is likely. Separations of more that 20 percent in a normal-sized placenta usually compromise the fetus, and separations of more than 50 percent can be lethal[44]. It has been estimated that up to 40 percent of all preterm deliveries are secondary to some form of acute abruption[5]. Premature placental separation can result in preterm delivery with all of the neonatal morbidity associated with prematurity. Fetal compromise can manifest as fetal heart rate deceleration, low APGAR scores, neonatal (hypoxic-ischemic) encephalopathy, and seizures. There may be other findings in the placenta to suggest fetal distress, including acute villous edema and significant meconium exposure. Acute abruption has an approximately ninefold relative risk for stillbirth [5]. Implications for the mother can include life-

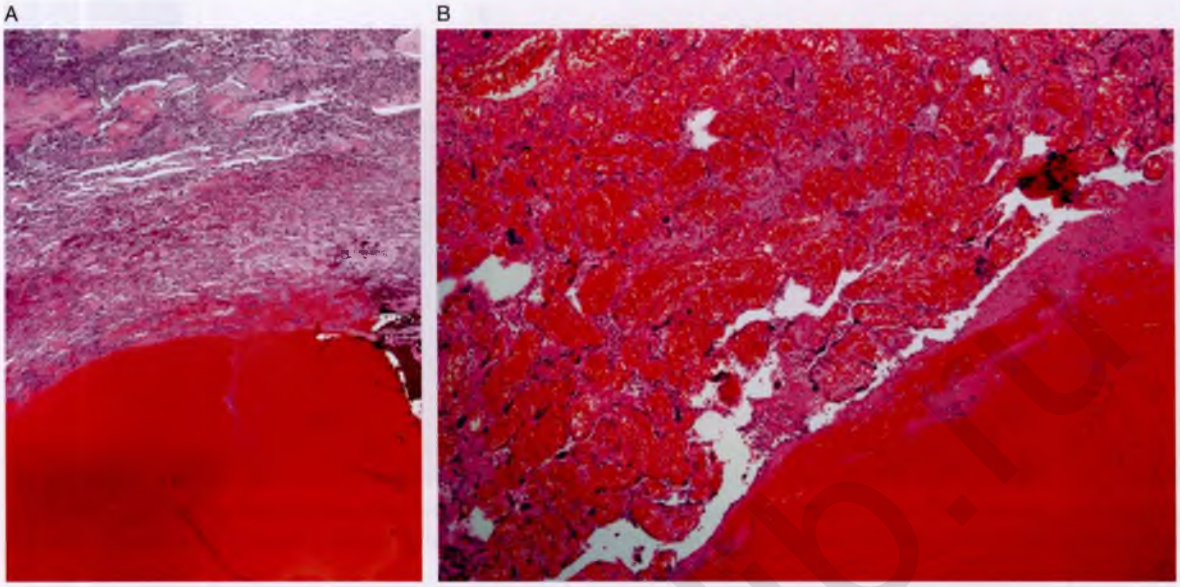

Figure 8.2 Acute abruption with (a) hemorrhage indenting the placenta and (b) associated recent intravillous hemorrhage.

threatening hemorrhage, DIC, uterine damage (so-called Couvelaire uterus), and the need for an emergent cesarean section. There is a known strong recurrence risk for abruption, being 10 times more common with a history of a previous abruption.[15,32] Cases can also cluster in families[39]. Women who have experienced acute abruption are at increased risk for developing cardiovascular disease later in life[45].

Knowledge Gaps: Timing of acute abruptio placentae relative to the time of delivery is often a clinical or legal question. There are a few reports that try to provide pathologic criteria, but the data is inconclusive[42]. This may be due to the difficulty in timing concealed abruptions and the differing biology between revealed and concealed abruptions (concealed abruptions are likely associated with localized pressure unrelieved by clinically evident bleeding). Further study is necessary to best describe the temporal progression of pathologic features of acute abruption. Two specific subcategories of acute abruptio placentae are poorly understood: acute abruptio placentae without underlying clinical risk factors, and recurrent acute abruptio placentae. Molecular studies on potential genetic causes of abruptions are needed.

Acute Marginal Abruption (Marginal Abruption, Marginal Sinus Thrombosis, Rupture of the Marginal Sinus, Acute Peripheral Separation)

Definition: Venous hemorrhage at the margin of the placenta

Clinical Context: The margin of the placenta is a hot spot for venous bleeding of unclear etiology. Marginal abruptions generally develop more slowly than acute abruptio placentae due to the lower pressure of a venous bleed. Most marginal abruptions are clinically silent and are only revealed with delivery when the placenta shows a marginal blood clot. They are often associated with acute chorioamnionitis, which can be either be a primary or secondary phenomena[8,16,34]. If associated with chorioamnionitis, the infection is usually clinically silent and only "picked up" pathologically[44]. Typically vaginally bleeding is not as catastrophic as the arterial hemorrhage associated with acute abruption (see "Acute Abruptio Placentae" above). Because of the location of the bleeding, the placental separation is typically partial and fetal compromise is often minimal. Marginal abruptions do not always precipitate delivery and can become "chronic."

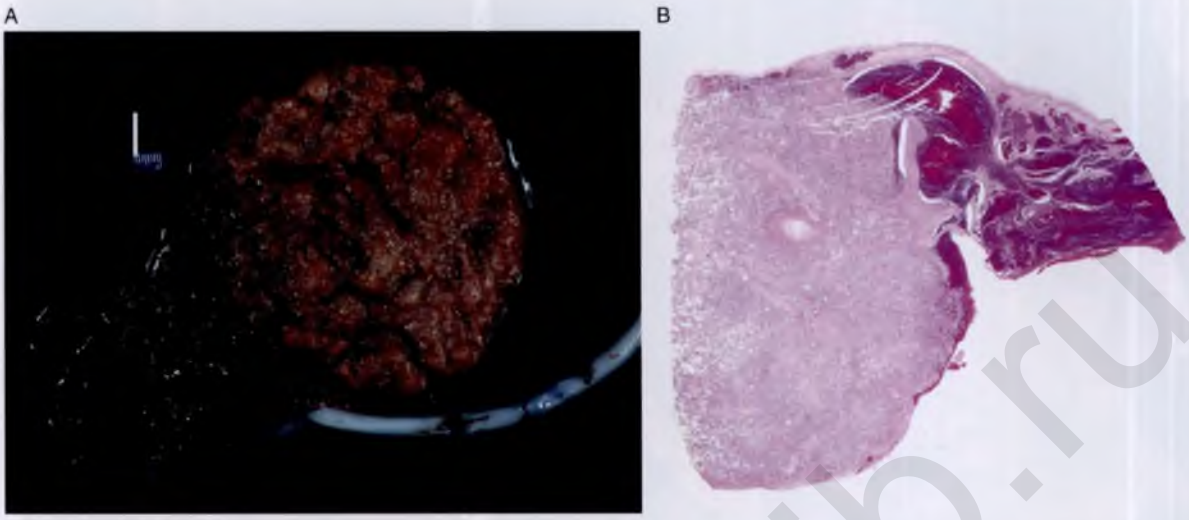

Figure 8.3 (a) Term placenta with marginal abruption. Note the hemorrhage extending from approximately 20–25 percent of the placental margin. (b) Histology of placenta showing dissecting hemorrhage through the placental margin (both courtesy of R. Redline).

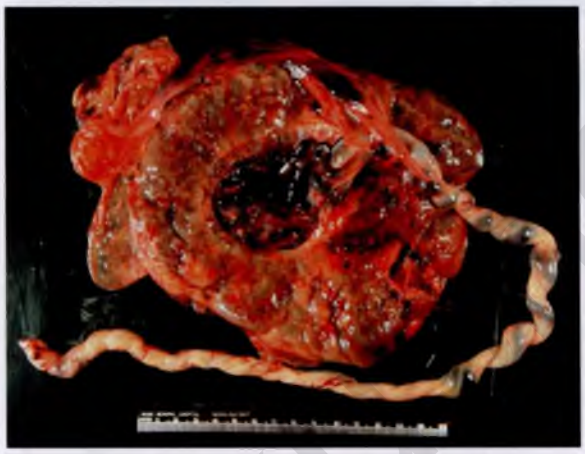

Figure 8.4 Gross photograph of a placenta with circumvallation. Note the inner "circle" of folded membranes around the umbilical cord insertion.

Proposed Pathogenesis: Venous disruption at the margin of the placenta resulting in hemorrhage that dissects often retromembranously and subchorionically. The etiology is not clear but may relate to abnormal implantation, inflammation, or trauma.

Gross Features: Typically, there is retromembranous and marginal hemorrhage/hematoma, sometimes with marginal indentation of the parenchyma (Figure 8.3). Marginal abruptions that occur early in gestation without delivery can become chronic and result in circumvallation or circummargination (Figure 8.4). Chronic marginal abruptions can also result in diffuse chorioamnionic hemosiderosis (DCH), a distinctive gross and histologic pathology in which the placenta has brown discoloration, often with a granular surface and circumvallation (Figures 8.5). Chronic abruption and DCH are discussed in more detail later in this chapter.

Microscopic Features: Acute marginal abruptions occur along the margin of the placental disk. Histologic findings include intervillous and subchorionic hemorrhage, often with admixed fibrin and acute inflammatory cells. Acute chorioamnionitis may be present and robust.

Ancillary Diagnostic Testing: No specific ancillary testing is useful in acute marginal abruptions. One may consider culturing the placenta for microbiologic studies, if there is gross evidence of acute chorioamnionitis.

Prognostic Implications: Marginal abruptions are indolent pathologies with complications based on whether or not separation leads to preterm delivery. If significant extension of the acute marginal abruption occurs, the prognosis is similar to that of acute abruptio placentae. Marginal abruptions may also progress to massive subchorial hematomas, also known as Breus' moles (see Chapter 18)[46]. Progression to chronicity can result in serious complications, including DCH or chronic abruption oligohydramnios syndrome (CAOS) (discussed below).

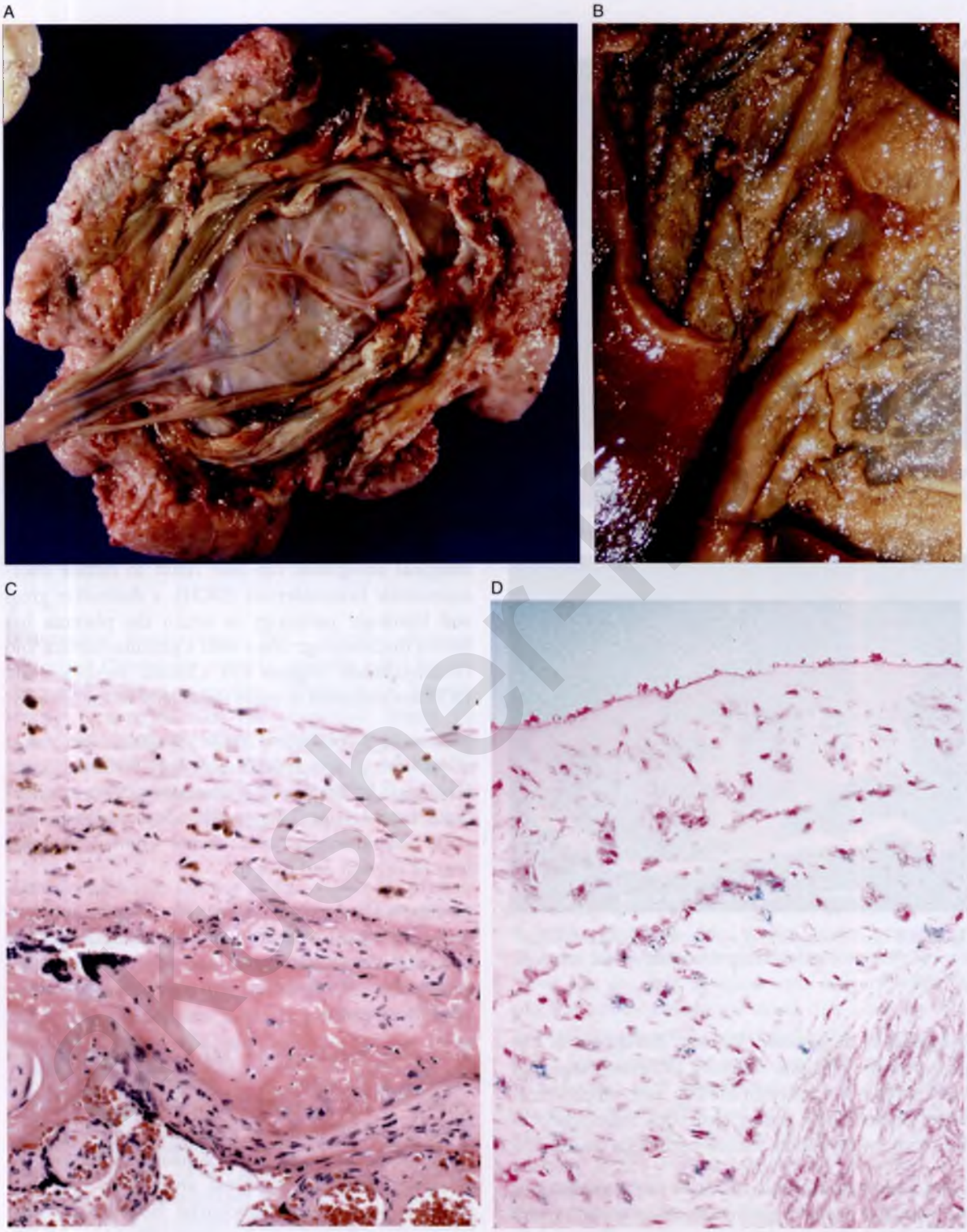

Figure 8.5 (a) Gross photograph of chronic abruption in a case of a preterm demise. Notice the discoloration and the circumvallation of the membranes (Courtesy of T. Boyd). (b) Closer view showing brown discoloration and granularity of the membranes in a separate case (Courtesy of J. Stanek). (c) Chorionic plate in a case of diffuse chorioamniotic hemosiderosis due to chronic abruption. Note the dark "chunky" pigment in more spindled macrophages. (d) Chorionic plate in a case of chronic abruption with diffuse chorioamniotic hemosiderosis (Prussian blue stain). Images (c) and (d) provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

Knowledge Gaps: Whether or not the acute chorioamnionitis often seen with marginal abruption is causal or coincidental is not clear (i.e. does the abruption weaken the membranes and result in rupture and contamination by cervicovaginal flora, or does acute chorioamnionitis associated with deciduitis result in weakening the decidual bed and thus lead to the marginal abruption?). These issues require further study.

Subacute Abruptio Placentae (Subacute Abruption, Old Abruption, Chronic Central Abruption)

Definition: Concealed or revealed placental separation that is non-acute. Generally these are separations that are incomplete and occur days to weeks before delivery.

Clinical Context: Subacute abruptio placentae occurs in clinical scenarios similar to acute abruptio placentae, but they are generally smaller and more confined; therefore, delivery does not rapidly follow.

Proposed Pathogenesis: Subacute abruptio placentae is thought to be due to arterial hemorrhage without delivery and with continuation of the pregnancy, often to term. Risks for subacute abruptio placentae include hypertensive diseases and abnormal placentation (e.g. placenta previa, shallow or deep implantation), but most are idiopathic.

Gross Features: A somewhat organized retroplacental hematoma with overlying placental infarction is typical (Figure 8.6). The hematoma is usually adherent to the parenchyma in contrast to acute abruption or acute marginal abruption in which the hemorrhage/hematoma can be easily "removed" from the parenchyma.

Figure 8.6 Gross photograph of a subacute abruption. Note the incompletely organized retroplacental hematoma with overlying placental compression and infarction.

Microscopic Features: Organizing retroplacental hematoma with indentation of the parenchyma, villous necrosis/infarction in a dome shape covering the hematoma. Rarely, subacute abruptio placentae can be associated with hemosiderin deposition in the adjacent decidua or membranes, but not usually to the extent needed for the diagnosis of DCH (see below).

Ancillary Diagnostic Testing: Not applicable.

Prognostic Implications: Prognosis depends on the placental reserve. Subacute abruptio placentae decreases the functional placental capacity; therefore, when occurring in small placentas, it can result in placental insufficiency and fetal compromise.

Chronic Abruption (Classic Chronic Abruption, Chronic Abruption Oligohydramnios Syndrome [CAOS], Circumvallation, Chronic Marginal Abruption, Diffuse Chorioamniotic Hemosiderosis [DCH], Chronic Peripheral Separation)

Clinical Context: Chronic abruptions typically present with longstanding bleeding during pregnancy, often for weeks to months. Oligohydramnios is often present – chronic abruption oligohydramnios syndrome (CAOS). Multiparity and tobacco smoking are associated with chronic abruption[47].

Proposed Pathogenesis: Placental separation due to venous bleeding, usually at the margin of the placenta, for an extended duration during pregnancy[47]. The etiology is poorly understood, and no clear risk factors are known. DCH is likely due to blood and blood breakdown products in the amniotic cavity secondary to "leakage" through the membranes from retromembranous/chorionic plate hematoma(s), although this has been disputed by some[48]. The mechanism of associated oligohydramnios is unclear but may be related to an increased incidence of PPROM/PROM via release of cytokines[10].

Gross Features: Circumvallate membrane insertion (circumvallation), partial or complete, is common. The presence of organizing marginal hematomas is characteristic. The gross phenotype can include a green-brown discoloration and sometimes

a granular-appearing placental chorionic surface (Figure 8.5a, 8.5b).

Microscopic Features: Marked chorioamnionic hemosiderin deposition (DCH) is often present and florid. Pigmented macrophages in DCH are more prominent in the chorionic plate than in the free membranes and often have a spindled phenotype with chunky brown pigment (Figure 8.5c), as compared to meconium-filled macrophages, which are more common in the membranes and are usually round with finer pigment (see Chapter 19). Iron is demonstrable by Prussian blue stain in most, but not all, cases with these findings (Figure 8.5d). Positivity is not required in otherwise typical cases to make the diagnosis. 47 The associated hematoma typically shows signs of organization.

Ancillary Testing: Iron stain is usually positive in DCH[47].

Prognostic Implications: Chronic abruption puts the pregnancy at risk for preterm delivery and thus perinatal complications[49]. DCH and CAOS have significant associations with perinatal morbidity and mortality[49–51]. Neurodisability, including cerebral palsy, has been associated with DCH in some[52,53], but not all[47,48] studies. Neonatal pulmonary hypertension and "dry lung" are both associated with DCH and chronic abruption[49–51]. The pathogenesis of the pulmonary pathology is unknown but presumed to be related to chronic in utero hypoxia[54].

Knowledge Gaps: DCH and CAOS can be associated with significant clinical sequelae of unclear pathogenesis, possibly related to antepartum hypoxia[54].

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Chapter 9

Fetal Stromal-Vascular Developmental Abnormalities

Raymond W. Redline

The placenta has two distinct compartments. The maternal-trophoblastic compartment establishes adequate placental attachment and access to maternal arterial blood flow. Lesions affecting this compartment are discussed in Chapters 5–8. The fetal stromal-vascular compartment extracts substrates through the "interhemal" trophoblastic barrier, delivers them to the developing conceptus, and returns catabolic waste products to the placenta for excretion. The structural elements constituting this compartment include the capillaries, arterioles, venules, and mesenchymal cells of the distal villi and the large non-gas-exchanging arteries, veins, and supporting stroma of the proximal villi and chorionic plate. Placental fetal stromal-vascular lesions can be separated into three subgroups: those related to variations in villous structure (developmental; this chapter), those attributable to obstructed blood flow (fetal vascular malperfusion; Chapter 10), and those associated with loss of circulatory integrity owing to either vascular disruption or tissue edema (Chapter 11). Fetal stromal-vascular developmental abnormalities reflect genetic, epigenetic, or environmental factors that alter the morphogenic relationships between trophoblast, fetal mesenchymal stroma, developing vessels, and resident tissue macrophages (Hofbauer cells).

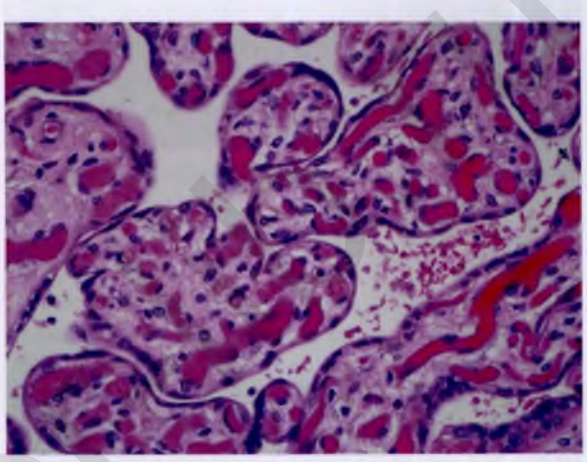

Figure 9.1 Villous chorangiosis. Clusters of terminal villi, all with 10 or more capillary cross-sections per villus.

CAPILLARY-VASCULAR LESIONS

Villous Chorangiosis (Villous Hypercapillarization or Hypervascularity)

Definition: An increased number of capillary cross-sectional profiles per villus: minimal criteria as per Altshuler – more than 10 capillaries per villus in 10 or more distal villi in several regions of the placenta (Figure 9.1)[1]. In most cases, occasional villi will show 15–20 capillaries or more.

Clinical Context: *Villous chorangiosis* is most common in term placentas and in two clinical scenarios: reduced intervillous oxygen tension with normal perfusion and poorly controlled maternal diabetes[2]. Clinical situations associated with intervillous hypoxemia include smoking, pregnancy at high altitude, high levels of air pollution, maternal anemia, and multiple gestation[3–7]. Abnormal vascular patterns, including chorangiosis and chorangiomatosis, may also accompany dysmorphic villi in cases with genetic and chromosomal abnormalities (see below)[8].

Proposed Pathogenesis: Chorangiosis is due to excessive elongation and branching of villous capillaries. These capillaries also show redundant intercapillary connections, a decreased proliferative rate, and immature phenotypic features[9,10]. Increased capillarization can begin early in the first trimester, as shown by comparison of first trimester terminations in smoking versus non-smoking mothers[11]. Hypervascularity in placentas delivered at high altitudes is associated with increased glutathione, but not elevation in markers of hypoxic stress such as HIF-1 alpha, suggesting that it represents a successful compensatory response to decreased intervillous oxygen

tension[12]. Chorangiosis in diabetes is believed to develop through a pathway of fetal hyperglycemia, increased placental insulin levels, and insulin/ IGF-1 receptor mediated angiogenesis.

Gross Features: Chorangiosis is often associated with placentomegaly, at least in part due to its increased frequency in diabetic pregnancies.

Microscopic Features: Increased capillary cross-sections are usually seen in contiguous groups of distal villi in the lower third of the placenta. Strict counting is necessary to overcome the subjective impression of increased density in congested capillaries, particularly at the periphery of placental sections. While chorangiosis can be combined with delayed villous maturation (see below), especially with maternal diabetes, villi are usually normal in this situation. Local increases in capillary density may also be seen near other villous lesions. However, diagnosis requires that chorangiosis be present in most or all sections and in areas far removed from foci of chronic villitis, avascular villi, or villous infarcts. Other lesions associated with chronically decreased intervillous oxygen tension, such as increased circulating nucleated red blood cells, can accompany chorangiosis (see Chapter 20). Chorangiosis is distinguished from chorangioma and chorangiomatosis by its diffuse nature, localization to distal villi, and absence of surrounding pericytes[8].

Ancillary Diagnostic Testing: Chorangiosis in association with placentomegaly and delayed villous maturation should prompt consideration of abnormal maternal glucose tolerance[13]. Placentas with marked chorangiosis in association with dysmorphic villi, particularly with fetal anomalies, may warrant investigation for underlying genetic/chromosomal abnormalities, including Beckwith-Wiedemann syndrome[14].

Prognostic Implications: In most recent studies, villous chorangiosis is not by itself a risk factor for adverse outcomes but rather a marker for decreased oxygen delivery and reduced placental reserve to withstand stress (so-called preplacental hypoxia). As such it is commonly seen in combination with other clinical conditions or placental lesions more directly associated with adverse outcomes such as stillbirth and neurodisability[15].

Knowledge Gaps: Risk factors for chorangiosis, chorangioma, and chorangiomatosis overlap, yet for unknown reasons these conditions do not commonly occur together[8]. Whether or not decreased intervillous oxygen tension and glucose intolerance work through a final common pathway to promote increased angiogenesis is not clear.

Chorangioma / Localized Chorangiomatosis (Placental Hemangioma, Recurrent Multiple Chorangioma Syndrome)

Definition: A benign vascular lesion, nodular or infiltrating multiple contiguous stem villi, composed of proliferating capillaries with surrounding pericytes and fibrous stroma.

Clinical Context: Chorangiomas may be seen in any placenta but have an increased incidence in multiple gestation and pregnancies complicated by preeclampsia[8,16]. They are most commonly seen in term or late preterm placentas. Chorangiomas may be linked to an increased incidence of vascular tumors and malformations in the infant[17,18]. A rare lethal syndrome is characterized by multiple chorangiomas of all sizes within villi throughout the placenta (see below)[19,20].

Proposed Pathogenesis: Chorangioma formation is believed to be triggered by reduced oxygen tension in areas containing large numbers of mesenchymal stem and/or endothelial progenitor cells (margins of chorionic plate and major stem villi)[8,21]. Whether they are clonal lesions has not been established. Their phenotype resembles infantile hemangiomas (positive expression of Glut-1 and other markers), lesions which are thought to form as a result of the dissemination of placental mesenchymal stem cells/endothelial progenitor cells into the fetal circulation during late gestation or parturition[22].

Gross Features: Chorangiomas are often incidental findings in random histologic sections. However, they are generally 2 mm or more in diameter and should be detectable by careful gross inspection. They are red-brown, nodular, have a smooth cut surface, and are usually found either at the placental margin or underneath the chorionic plate. Large ("giant") chorangiomas have been defined as greater than 3.0 cm and can be associated with fetal complications as detailed below (Figure 9.2).

Microscopic Features: Chorangiomas are nodular lesions composed of an anastomosing network of

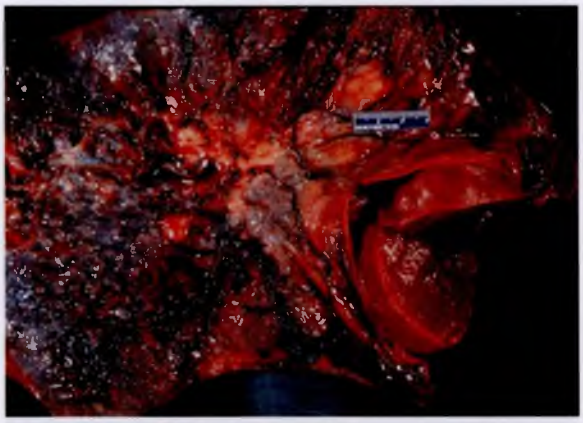

Figure 9.2 Large placental chorangioma (bisected). Well-circumscribed solid lesion located eccentrically just below the chorionic plate.

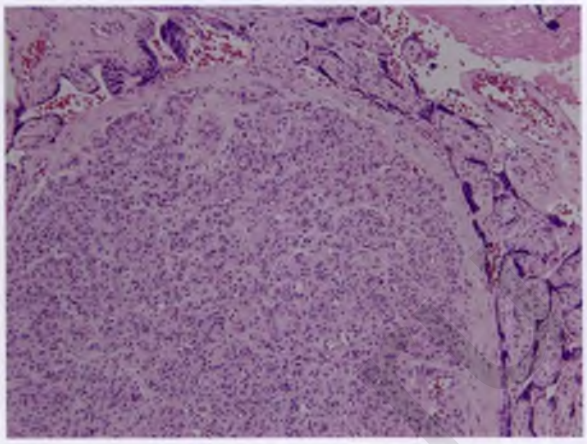

Figure 9.3 Placental chorangioma. Network of endothelial lined vascular channels with adjacent pericytes surrounded by supportive fibroblastic stroma and syncytiotrophoblast. Larger feeding vessels are seen at the top of the lesion.

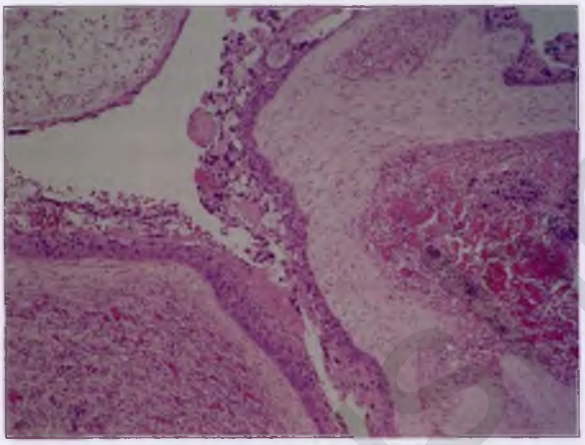

Figure 9.4 Nonspecific trophoblast hyperplasia surrounding placental chorangioma. Proliferative trophoblast surrounding chorangioma show hyperplasia without the atypia, necrosis, and solid growth seen with choriocarcinoma.

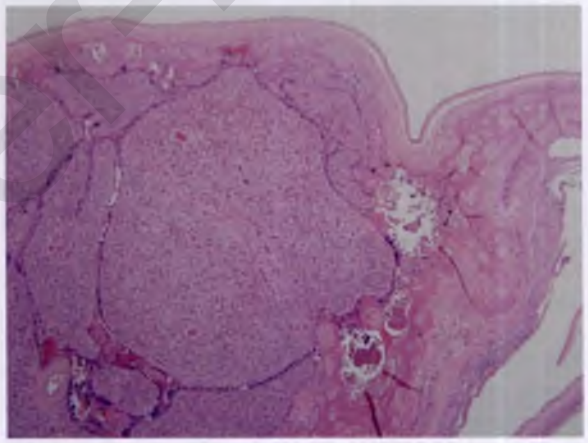

Figure 9.5 Localized chorangiomatosis ("wandering chorangioma"). Chorangiomatous proliferation localized to one group of contiguous primary stem villi.

prominent capillaries with surrounding pericytes and embedded in a collagenous stroma of fibroblasts and macrophages (Figure 9.3). In some cases, the fibrous stroma predominates. Occasionally, the lesions show hemorrhagic infarction and global ischemic necrosis, which can mimic villous infarction. Approximately 40 percent of chorangiomas are surrounded by a layer of proliferative villous trophoblasts that can be confused with an intraplacental choriocarcinoma (Figure 9.4) (see Chapter 4)[23]. The term "chorangiocarcinoma" has been used in a few case reports, but there is no evidence of any subsequent malignant behavior[24]. Localized chorangiomatosis is essentially a "wandering" chorangioma that has spread into contiguous large stem villi rather than forming a single expansile nodular lesion (Figure 9.5)[8]. It has the same gross and histologic appearance and the same clinical associations as chorangioma, and it should be considered as essentially the same lesion. Placentas with a chorangioma have an increased prevalence of changes consistent with maternal vascular malperfusion[25].

Ancillary Diagnostic Testing: Reticulin and immunohistochemical stains for pericytes (muscle-specific

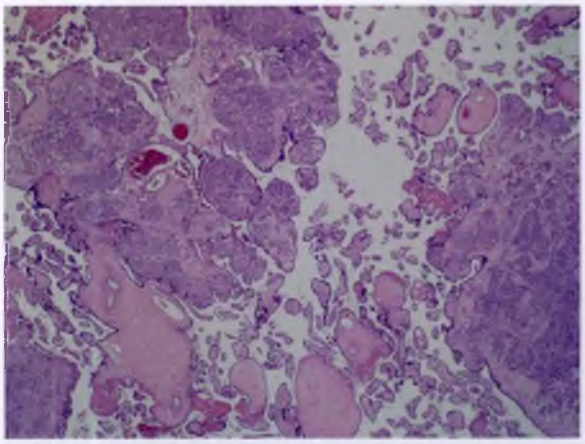

Figure 9.6 Recurrent multiple chorangioma syndrome. Numerous small islands of chorangiomatous tissue nesting in proximal and distal villi throughout the placenta.

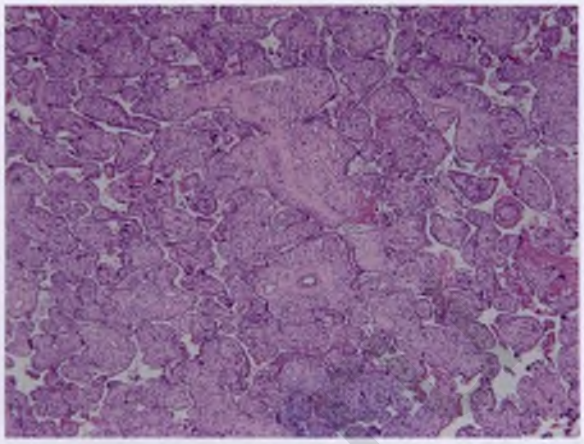

Figure 9.7 Multifocal chorangiomatosis. Multiple patchy areas throughout the placenta show a loosely organized network of anastomosing small vessels and pericytes surrounding large vessels in stem and immature intermediate villi.

actin) can distinguish between chorangiosis and chorangioma in problematic cases[8,26].

Prognostic implications: Large/giant or even intermediate-sized chorangiomas have been associated with FGR or stillbirth[26,27]. Occasionally, fetuses develop hydrops fetalis due to AV shunting or DIC (Kasabach-Merrit syndrome) secondary to platelet sequestration within the tumor[28]. Recurrent multiple chorangioma syndrome is a rare, presumably genetic, syndrome of unknown etiology that can lead to stillbirth in multiple pregnancies (Figure 9.6)[19,20]. The responsible gene has not been identified.

Knowledge Gaps: The relationship between chorangioma and chorangiosis remains poorly understood. These lesions rarely overlap but can occur together in Beckwith-Wiedemann syndrome[29]. Details of the pathogenesis in terms of cell of origin, initiating events, clonality, and genetic predisposition remain unclear.

Multifocal Chorangiomatosis (Diffuse Chorangiomatosis, Diffuse Multifocal Chorangiomatosis)

Definition: Foci of excessive capillary growth characterized by a network of small anastomosing vessels at the margins of stem and/or immature intermediate villi. Endothelial cells within the lesion are surrounded by pericytes and stromal cells that impart an appearance similar to chorangioma (see above). However, foci of chorangiomatosis are not sharply circumscribed and are distributed throughout the placenta.

Clinical Context: In comparison to chorangiosis and chorangiomas, multifocal chorangiomatosis (MC) is more common in early preterm deliveries and is associated with older maternal age, non-African-American ancestry, and multiparity[8,30]. There is no documented association with preeclampsia, multiple gestation, diabetes, or conditions predisposing to intervillous hypoxia. Distinct subgroups are associated with congenital malformations, fetal growth restriction, and stillbirth. An association of both chorangiosis and chorangiomatosis with alcoholism drug abuse has also been noted[8,31].

Proposed Pathogenesis: Limited data suggest an anomalous proliferative response within the paravascular capillary network surrounding immature intermediate and stem villi. Initiating events, at least in some cases, may relate to fetoplacental developmental abnormalities and/or abnormal fetal blood flow.

Gross Features: No known associated gross features.

Microscopic Features: MC is characterized by a network of small anastomosing vessels along the margins of stem and immature intermediate villi that contain central muscularized vessels (Figures 9.7 and 9.8).

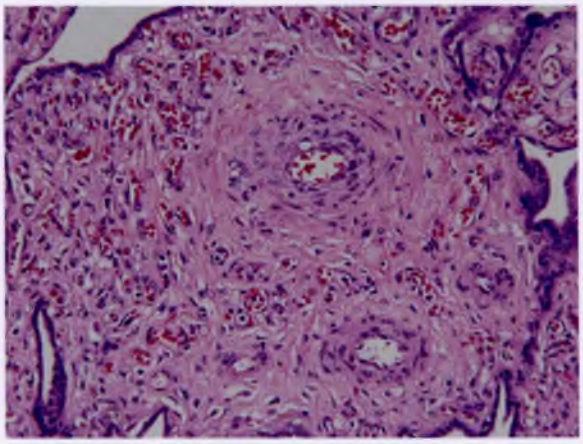

Figure 9.8 Multifocal chorangiomatosis. Higher-power image showing the extent of vascular proliferation within the "paravascular net" of a proximal stem villus.

Distal villi in cases of MC sometimes show delayed villous maturation or coexisting chorangiosis. Other associated histologic findings include small foci of avascular villi, fetal arteriolar hypertrophy, and irregular villous contour. Two broad subgroups have been distinguished: patchy MC with multiple small foci, most occupying less than a 10X microscopic field, and extensive MC with more diffuse areas of involvement, at least one of which exceeds a 4X microscopic field. Cases associated with abnormal villous contour and/or trophoblast inclusions overlap with dysmorphic villi (discussed below).

Ancillary diagnostic testing: Karyotype and genetic counseling should be considered in severe cases and/or adverse outcomes.

Prognostic Implications: Patchy MC has been associated with prematurity and fetal growth restriction; extensive MC with macrosomia, congenital anomalies, and stillbirth[30,32]. Underlying genetic/chromosomal abnormalities, including Beckwith-Wiedemann syndrome, and undiagnosed fetal congenital anomalies should be excluded in severe cases.

Knowledge Gaps: MC is relatively uncommon and poorly understood. Additional study is needed to understand to what extent its pathogenesis overlaps with chorangiosis, chorangiomas, and dysmorphic villi.

STROMAL-ARCHITECTURAL ABNORMALITIES

Delayed Villous Maturation (Distal Villous Immaturity, Maturation Defect, Villous Dysmaturity, Variable Maturation)

Definition: A patchy to diffuse increase in the proportion of distal villi in term or late preterm placentas with some or all of the following characteristics: increased villous diameter, increased stromal cellularity, nonperipheral capillaries, a thickened layer of villous trophoblast with uniformly distributed syncytiotrophoblastic nuclei, persistent cytotrophoblast, and a paucity of vasculosyncytial membranes[33].

Clinical Context: Delayed villous maturation (DVM) is increased in diabetic pregnancy, especially gestational or type 2 diabetes[34,35]. It is also more common with excessive pregnancy weight gain and fetal macrosomia in the absence of maternal glucose intolerance [36]. A distinct subgroup of cases has been attributed to chronic umbilical cord occlusion, such as that seen with hypercoiling[37]. Histologic criteria, if any, distinguishing the latter from cases associated with diabetes have not been published. Rare cases may present with FGR. In these cases, there is a decrease in distal villous branching[38].

Proposed Pathogenesis: DVM is a derangement of normal villous maturation and development. In part, this lack of terminal differentiation may be attributed to continuing villous growth. Some authors have proposed an absolute block in the capacity to convert immature intermediate villi to mature intermediate and terminal villi, particularly in cases associated with stillbirths – sometimes recurrent[39]. Increased villous growth factors such as fetal insulin in diabetes and increased venous pressure due to chronic umbilical cord obstruction with hypercoiling are implicated by virtue of their strong clinical associations with DVM[40].

Gross Features: Placentas with DVM are often large and pale. Regardless of absolute size, they tend to have a decreased fetoplacental weight ratio. Hypercoiling and other obstructive umbilical cord lesions (see Chapter 16) should be excluded by gross examination.

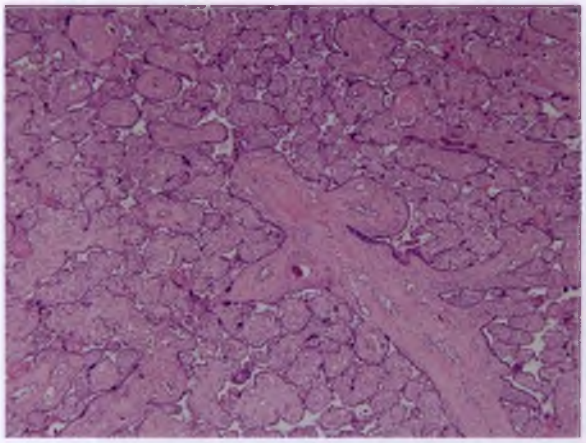

Figure 9.9 Delayed villous maturation, term placenta. Low-power image showing enlarged branching distal villi with increased stroma and a continuous layer of cellular trophoblast.

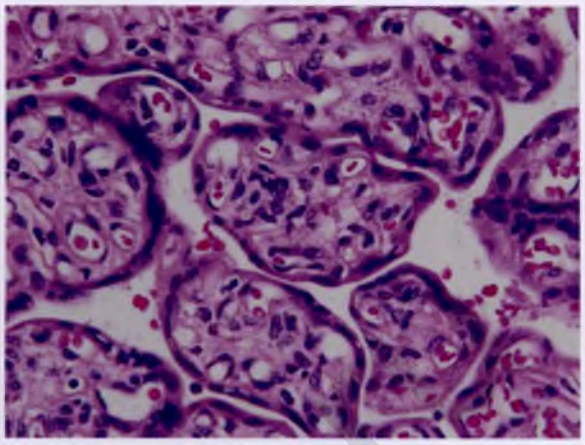

Figure 9.10 Terminal villi with delayed maturation, term placenta. High-power image demonstrating thick cellular trophoblast, central capillaries, increased stromal cells, and lack of intimate contact between the capillary endothelium and adjacent syncytiotrophoblast.

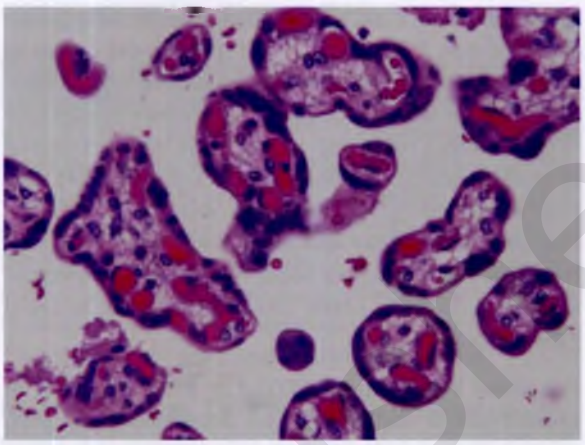

Figure 9.11 Mature terminal villi, term placenta. Villi show scant stromal cells and multiple capillaries interfacing with attenuated areas of overlying syncytiotrophoblastic cytoplasm without intervening nuclei (vasculosyncytial membranes).

Microscopic Features: DVM is characterized on low-power magnification by enlarged, pale-staining distal villi within the lower two-thirds of the placenta that seem to efface the intervillous space (Fig 9.9). At higher magnification, these distal villi resemble immature intermediate villi, which are uncommon in placentas after 30 weeks. In contrast to normal mature terminal villi, they have an increased amount of cellular sometimes edematous stroma, a thick layer of syncytiotrophoblast with an increased number of uniformly distributed nuclei, scattered persistent cytotrophoblast, and nonperipheral villous capillaries that fail to merge with the overlying syncytiotrophoblast to form vasculosyncytial membranes (Figures 9.10, 9.11). DVM may be patchy to diffuse (diffuse = affecting 30 percent of 1 slide or lesser degrees of involvement in all slides) or more localized (focal = less than 30 percent in each slide and not present in all slides). The differential diagnosis includes villous edema in hydrops fetalis and chronic inflammation in VUE (see Chapters 11 and 13). Whether delayed villous maturation develops due to edema in hydrops is controversial, but a recent paper suggests that term placentas delivered long after successful treatment of hydrops by intrauterine transfusion show a pattern of delayed villous maturation[41]. DVM can also be an additional feature in placentas with chorangiosis or one of the dysmorphic patterns described below. Some features of maternal malperfusion such as increased syncytial knots and increased intervillous fibrin may accompany DVM, particularly with long-standing type 1 diabetes (Figure 9.12). This pattern has been termed "variable maturation" or "villous dysmaturity," with the former being preferred as a less ambiguous term[42]. Reproducibility of diagnosis for DVM is an ongoing challenge, but studies suggest that at least some observers can attain a high degree of agreement[43]. A useful habit that can assist in the evaluation of both delayed and accelerated villous maturation is to routinely state the observed pattern of villous maturation in all placental reports (very immature = expected for <24 weeks; immature =

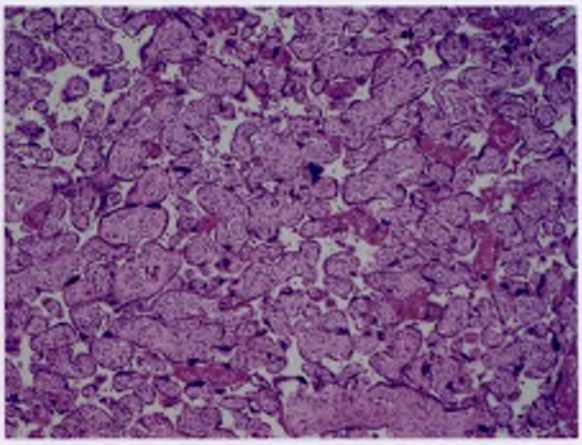

Figure 9.12 Delayed villous maturation with focally increased syncytial knots and intervillous fibrin (variable maturation/villous dysmaturity), term placenta.

expected for <30 weeks; slightly immature = expected for <37 weeks; mature = expected for 37 weeks and beyond)[33]. Variation from the expected can then be indicated by using the phrase "histologically mature or immature" in the initial diagnostic line as appropriate.

Ancillary Diagnostic Testing: CD15 staining of small vessels has been proposed as a specific marker for DVM[44]. Limited experience limits conclusions as to its diagnostic utility at this time. Morphometric or semiquantitative confirmation of the absolute number of vasculosyncytial membranes has been used diagnostically in some centers[45]. However, this approach is time-consuming and may not account for the patchy distribution seen in many cases.

Prognostic Implications: DVM may reduce placental reserve by increasing the diffusion distance and impairing gas exchange at the interhemal membrane. It has been associated with stillbirth and an increased risk of neonatal encephalopathy[35,46]. While many cases are associated with macrosomia and relative placentomegaly, a distinct subgroup has FGR and relatively normal placental weights. The recurrence rate has been estimated at 10 percent[47].

Knowledge Gaps: Interobserver variability and regional variations in diagnostic criteria have hindered attempts to dissect the relative roles of glucose intolerance, increased placental growth factors, increased intraplacental venous pressure, and genetic/epigenetic factors in causing DVM[43]. It is possible that DVM may eventually be separated into distinct pathophysiologic subgroups. Priorities are to establish more objective criteria for diagnosis in order to increase reproducibility.

Dysmorphic Villi (Atypical Villus Morphology, Irregular Villous Contour, Trophoblast Inclusions, Nonspecific Trophoblast Hyperplasia, Abnormal Distal Villous Vascular Pattern, Proximal-Distal Villous Discordance)

Definition: Focal or diffuse alterations in villous architecture and vascular patterning recapitulating those seen in early pregnancy specimens with known genetic/chromosomal abnormalities (see Chapter 3)[48–53].

Clinical context: Dysmorphic villi are understudied in late pregnancy specimens. Aside from an obvious connection with known fetoplacental genetic or chromosomal abnormalities, some evidence suggests associations with FGR with normal Doppler studies, risk of neurodevelopmental abnormalities, and placenta accreta[38,54,55]. Artificial reproductive technologies have an increased incidence of Beckwith-Wiedemann syndrome (BWS) and other genetic imprinting abnormalities that can also demonstrate dysmorphic villi[56].

Proposed Pathogenesis: Processes that could potentially cause dysmorphology limited to the placenta include confined placental mosaicism, placental chimerism, epigenetic modifications affecting only placental gene expression, or placenta-specific mutations that are silent in the fetus. Despite its reported frequency, pathologic findings related to confined placental mosaicism remain incompletely characterized[57–59]. All of the processes listed above could act at a cellular level by altering the balance between tissue morphogens, relative proliferative rates, and cellular differentiation. A possible morphogenetic mechanism for how this might occur for one dysmorphic lesion, trophoblast inclusions, is described below.

Gross Features: Placentas with dysmorphic villi are often either small or large for gestational age. Placentomegaly is a typical feature of BWS syndrome, which often shows dysmorphic features.

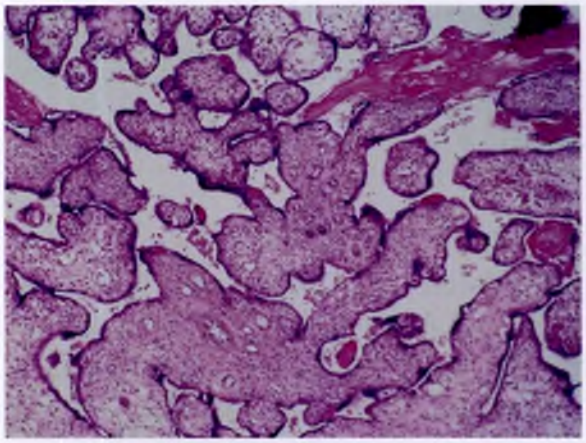

Figure 9.13 Dysmorphic villi: irregular villous contour and trophoblast inclusions. Distal villi show an increase in stroma and a lack of terminal villous development in addition to an irregularly irregular contour and multiple trophoblast inclusions (center).

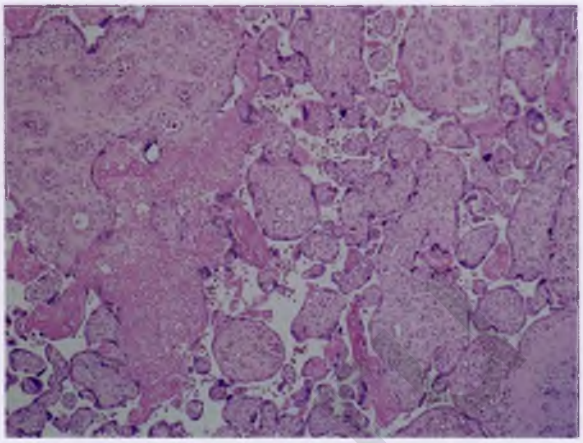

Figure 9.14 Dysmorphic villi: abnormal distal villous vascular pattern. Distal villi show increased number of irregularly distributed arterioles, small venules, and villous capillaries.

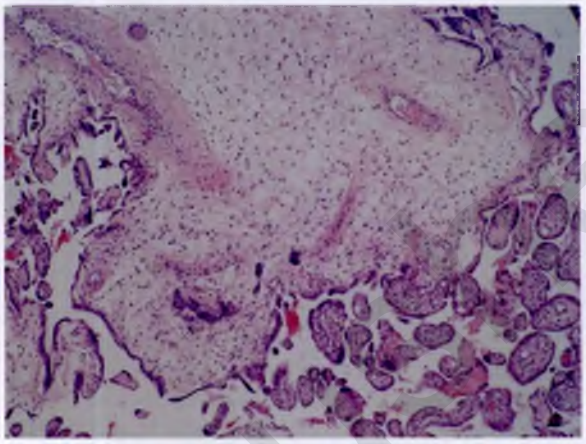

Figure 9.15 Dysmorphic villi, proximal-distal villous discordance, proximal edema/distal syncytial knot pattern. Early third trimester placenta with an edematous stem villus containing trophoblast inclusions and small distal villi with accelerated villous maturation with increased syncytial knots.

Microscopic Features: Irregular villous contour refers to scalloping and fjord-like invaginations affecting the entire distal villous tree and is often accompanied by trophoblast inclusions (Figure 9.13). The outline is best described as irregularly irregular, meaning that both large and small areas of scalloping are noted. Trophoblast inclusions, in some cases, may simply represent oblique sections of areas with irregular villous contour. However, Kliman favors that most are true epithelial inclusions, possibly forming due to a process of budding off from villous trophoblast due to uneven proliferative rates that favor cytotrophoblast over syncytiotrophoblast[60]. Nonspecific trophoblast hyperplasia has been reported with several distinct chromosomal anomalies, including trisomies 7, 15, and 22, monosomy X, and diandric triploidy[49]. This finding is more common in early pregnancy losses and is also discussed in Chapter 3. The trophoblast hyperplasia surrounding some chorangiomas (described above) is one example of this process in later pregnancy (Figure 9.4). Abnormal distal villous vascular pattern can present as a maze-like capillary network, dilated venous sinusoids, or anomalous large muscularized vessels within distal villi (Figure 9.14). Abnormal vascular pattern may be combined with or represent an exaggeration of the more common villous capillary lesions described above. Finally, a distinct abnormality in the number and morphology of proximal and distal villi (proximal-distal villous discordance) can take two forms: large edematous proximal villi with truncated distal villi showing accelerated villous maturation (Figure 9.15) and normal proximal villi with uniform undergrowth of distal villi showing either appropriate or delayed maturation for gestational age (Figure 9.16). A word of caution is necessary – a thorough familiarity with the range of normal villous morphology in placentas from both liveborns and stillborns of all gestational

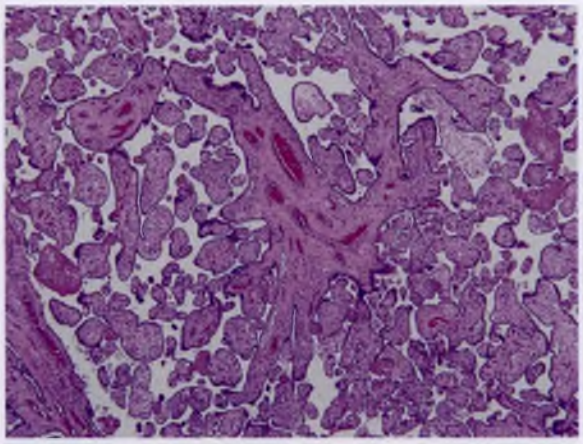

Figure 9.16 Dysmorphic villi, proximal-distal villous discordance (NOS). Abnormally small term placenta with delayed villous maturation, large proximal villi, and reduced branching of hypoplastic distal villi.

ages is necessary to avoid overcalling or undercalling these lesions[61].

Ancillary Diagnostic Testing: There are no simple, routinely available tests for further workup. Genetic studies including conventional karyotyping, array comparative genomic hybridization, DNA methylation profiling, and whole genomic/exomic sequencing could all potentially be applied to study these cases. Problems include heterogeneity of the dysmorphic changes within the placental parenchyma, expense, and lack of impact on clinical management.

Prognostic Implications: Dysmorphic villi are potential sentinels of abnormal development in the fetus. For example, one study reported an association with autism spectrum disorders[54]. To what extent they may contribute to other disease of childhood or adulthood is unknown, as is their recurrence risk in subsequent pregnancies.

Knowledge Gaps: Mechanistic studies are needed. A role for epigenetic modifications is perhaps most promising, but further investigation of confined placental mosaicism is also needed. Delineation and dissemination of specific diagnostic criteria to pathologists and careful analysis of clinical presentations, associated long-term outcomes, and recurrence risks are all priorities.

Placental Mesenchymal Dysplasia (Placental Vascular Anomaly with Diffuse Mesenchymal Stem Villous Hyperplasia, Pseudo-Partial Mole, Androgenetic Biparental Mosaic Chimerism with or without Complete Hydatidiform Mole)

Definition: Abnormal placenta, often enlarged, with segmental areas showing excessively dilated tortuous chorionic plate vessels and enlarged abnormal proximal villi showing cystic dilatation, fibroblastic stromal overgrowth, and vascular abnormalities affecting vessels of all caliber. Occasional cases may contain areas of complete hydatidiform mole.

Clinical Context: Placental mesenchymal dysplasia (PMD) may be detected by ultrasound after 8 weeks as a thickened placenta with subchorionic hypoechoic/cystic areas and reduced blood flow[62]. High rates of associated FGR (50 percent) and stillbirth (36 percent) have been noted[63]. Over 80 percent of infants are female; 20 percent have BWS. A small percentage of non-BWS cases develop extraplacental lesions (hepatic mesenchymal hamartoma, multiple hemangiomas, and other rare autosomal recessive conditions) related to an abnormal mosaic extraplacental clone (see below).

Proposed Pathogenesis: PMD results from populations of placental cells that fail to express one or more paternally imprinted genes at the chromosome 11 p15.2 locus. Most cases are secondary to androgenetic biparental mosaicism/chimerism (ABMC) deriving from an abnormal initial division of the fertilized egg in which the female genome fails to duplicate, leaving 1 normal biparental daughter cell and another with only paternally derived chromosomes[64]. Since YY androgenetic cells are nonviable, all cases of ABMC derived by this mechanism are female. Extent of placental involvement and occasional mosaic involvement of the fetus (see below) in ABMC depends on the relative viability and function of the androgenetic clone. The abnormal clone in ABMC is usually restricted to villous mesenchyme (stroma and vessels). However, rare polyphenotypic conceptuses can show mixtures of androgenetic trophoblast (complete hydatidiform mole), androgenetic mesenchyme (PMD), and biparental normal villi as defined by p57 immunohistochemistry (see below)[66,67]. Other

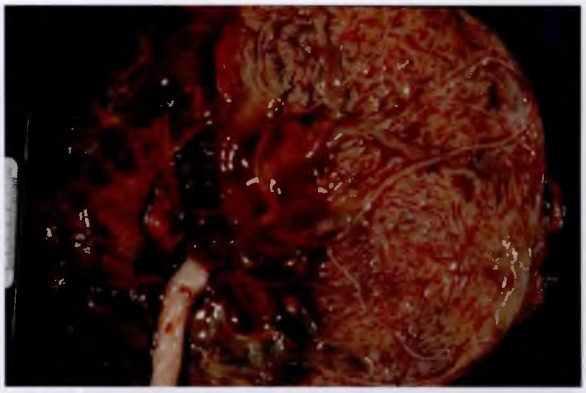

Figure 9.17 Placental mesenchymal dysplasia, chorionic plate. The far right portion of the chorionic plate is normal. The remainder shows cysts, dilated ectatic chorionic vessels, and recent subamnionic hemorrhage reflecting the tearing of abnormal vessels after delivery of the infant.

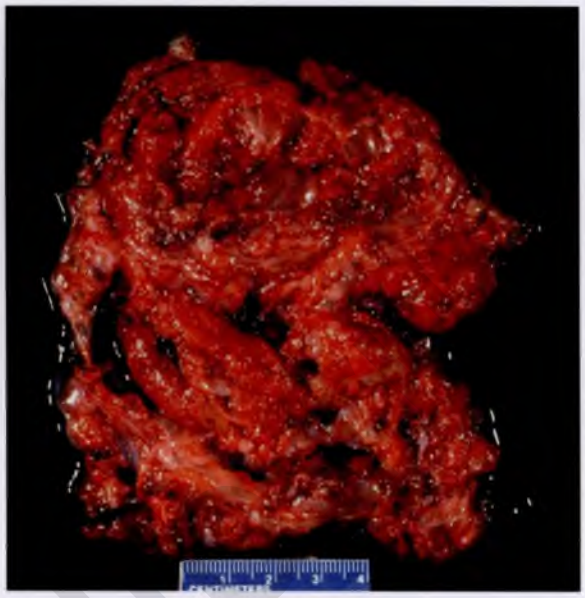

Figure 9.18 Placental mesenchymal dysplasia, basal plate. The maternal surface is somewhat discohesive, with multiple large protruding cysts. Image provided with permission by R. Redline, University Hospitals Cleveland Medical Center, Cleveland, OH.

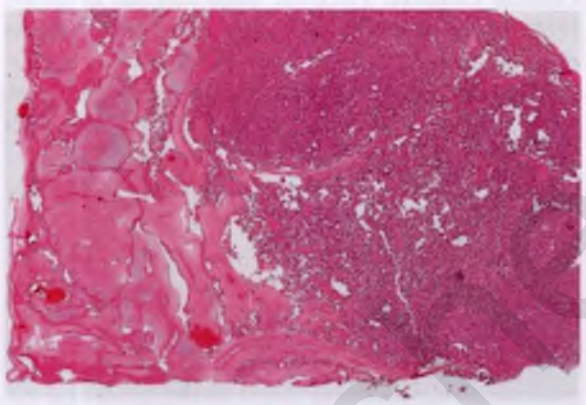

Figure 9.19 Placental mesenchymal dysplasia (whole slide image). Large stem villi on the left show fibrosis, myxoid change, and abnormal large vessels.

causes of PMD, some involving males, are BWS with paternal uniparental disomy for chromosome 11 p15.2, and transient neonatal diabetes with paternal uniparental disomy for chromosome 6, a condition that also affects gene expression from the chromosome 11 p15.2 IC1 region[65]. Cases of BWS with PMD all appear to have abnormalities affecting BWS imprinting center 1 (IC1). BWS associated with IC2 abnormalities appear to have a different placental phenotype (increased perivillous fibrin with atypical EVT; see Chapter 5). All causes of PMD share overexpression of IGF2, amongst other abnormalities.

Gross Features: Placentas with PMD are usually large for gestational age, occasionally exceeding 1,000 grams. The umbilical cord is thick and often hypercoiled (see Chapter 16). The fetal surface shows focally tortuous, thick-walled vessels with decreased branching and areas of aneurysmal dilatation that may occasionally rupture (Figure 9.17)[68]. Basal plate and cut surface show variable numbers of enlarged stem villi with multiple central cystic cavities extending throughout the parenchyma (Figure 9.18). Abnormal villi tend to have a patchy segmental distribution (Figure 9.19). Intervening areas are normal. Nodular lesions representing chorangiomas may sometimes be present.

Microscopic Features: The fibroblastic stroma of proximal villi is increased with areas of myxoid change and foci of cavitation that form central cisterns (Figure 9.20). Areas of PMD are sharply demarcated from adjacent normal villous parenchyma with no transitional zone. Fetal vascular abnormalities affect the chorionic plate and proximal villi. Large vessels in the chorionic plate and major stem villi are enlarged, irregularly dilated, variable in thickness, and increased in number. Smaller vessels in the remainder of proximal villi show a mixed pattern resembling, but more extreme than that seen in chorangiosis and chorangiomatosis (Figure 9.21). Abnormal fetal vascular architecture and parenchymal distortion can lead to thrombosis

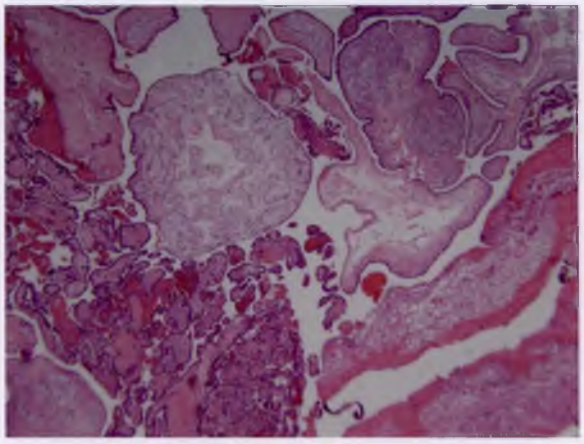

Figure 9.20 Placental mesenchymal dysplasia, cysts and stromal overgrowth. Normal term villi at the lower left are sharply demarcated from enlarged, edematous/myxoid villi with central cisterns on the right.

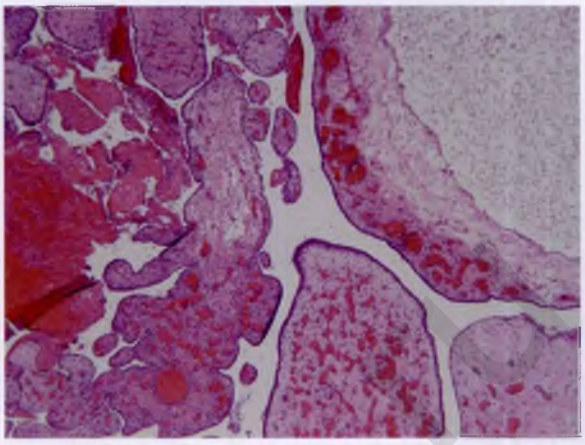

Figure 9.21 Placental mesenchymal dysplasia, abnormal vascular pattern. Large anastomosing networks of thin-walled vessels are seen in villi with both stromal overgrowth and central cisterns.

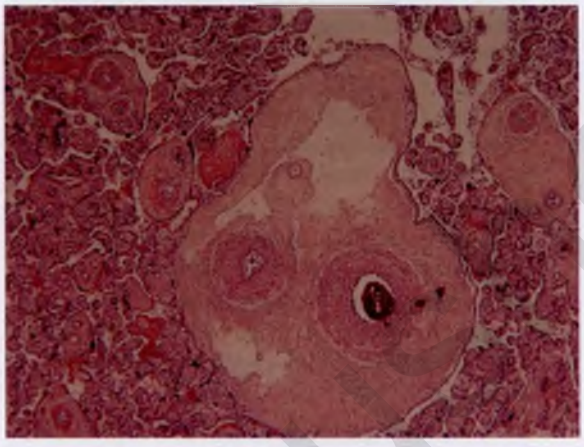

Figure 9.22 Possible early/focal placental mesenchymal dysplasia. This term placenta had 4 separate foci showing ectatic cisterns within otherwise normal stem villi. The infant developed cerebral palsy.

with extensive downstream avascular villi. Entities in the differential diagnosis include the following: late triploid partial hydatidiform moles that show a dimorphic population of cystic and small villi, all dysmorphic, with areas of trophoblast hyperplasia and irregular villous contour (see Chapter 4); late complete hydatidiform moles that have a single population of molar villi with uniformly marked trophoblast hyperplasia (see Chapter 4); and twin pregnancies with one complete mole that shows a sharply demarcated cystic component and, up on gross examination, that is confined to the edge of the otherwise normal other twin placenta. Histologically, the molar villi may be necrotic but lack fetal vessels and often show foci of residual trophoblast hyperplasia (see Chapter 4). In the rare cases of ABMC with areas of complete mole, the two components can be distinguished on the basis of histology (presence or absence of trophoblast hyperplasia and fetal blood vessels) and p57 immunostaining (see below)[66,67]. Chorionic cysts can mimic PMD clinically, but are composed of fibrinoid and transitional/immature EVTs (see Chapter 5)[69]. Occasional placentas showing irregular cysts within stem villi might represent very focal examples of PMD (Figure 9.22)

Ancillary Diagnostic Testing: Molecular testing to quantify and further characterize the androgenetic clone in PMD is only performed in a research context. Immunohistochemical studies using the monoclonal antibody p57 (also known as KIP2) highlight nuclei expressing the paternally imprinted CDKN1C gene located in the p15.2 region of chromosome 11[66]. Normal placental tissue and partial moles show diffuse staining of all cells (Figure 9.23). Staining is absent from villous stromal cells in the affected regions of PMD, but retained in villous cytotrophoblast (Figure 9.24). Complete moles lack p57 staining in both cytotrophoblast and villous stromal cells (see Chapter 4). Infants with PMD plus one of more of the following abnormalities, macrosomia, macroglossia, hemihypertrophy, and omphaloceles, should undergo molecular evaluation for BWS[70].

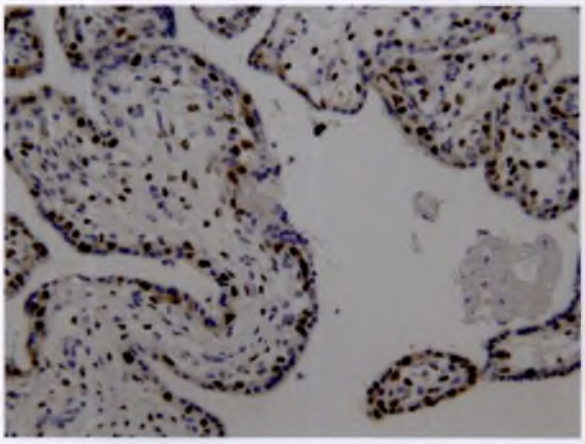

Figure 9.23 Normal placental villi, p57 immunostain. Cytotrophoblast and villous stromal cells express p57, suggesting a normal maternally derived chromosome 11.

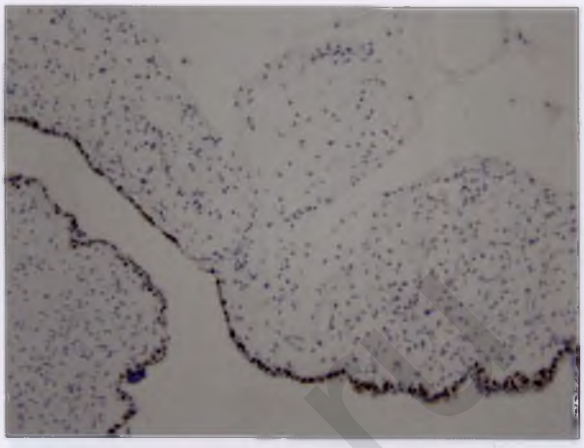

Figure 9.24 Placental mesenchymal dysplasia, p57 immunostain. Expression of p57 is lost in the stroma of villi with PMD/ABMC (absence of maternal chromosome 11). Villous cytrophoblastic expression is preserved.

Prognostic Implications: PMD is associated with an increased risk of FGR, stillbirth, and neonatal death[63]. Infants with BWS syndrome may present with specific congenital anomalies and are at risk for embryonal tumors and later renal disease[71]. Although generally sporadic, some cases of PMD associated with BWS recur in subsequent pregnancies. The androgenetic clone in PMD with PBMC can occasionally be expressed in the fetus, where the abnormal cells can form hepatic mesenchymal hamartomas and vascular hemangiomas[72].

Knowledge Gaps: The mechanisms explaining why the androgenetic cells in PMD are restricted to the mesenchymal lineage while those in complete hydatidiform mole also include villous trophoblast are unclear. Some cases of PMD may represent other undefined genetic or epigenetic abnormalities.

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Chapter 10

Fetal Vascular Malperfusion

Theonia K. Boyd

Fetal Vascular Malperfusion (Fetal Vessel Thrombosis, Fetal Thrombotic Vasculopathy, Fibrinous Vasculosis, Hemorrhagic Endovasculitis, Thrombosclerosing Placentitis)

Definition: Features as listed below by site and combined under the umbrella of fetal vascular malperfusion (FVM), are due to nonacute restriction in fetal blood flow within the placental-umbilical cord-fetal circuit. Synonyms in parentheses are included for correlation with the historical literature, but are discouraged for the sake of universal terminology.

Range of features in chorionic and/or stem fetal vessels:

- Vascular ectasia
- Thrombosis (recent to remote)
- Intramural fibrin deposition (intimal fibrin cushion)
- Stem vessel obliteration (fibromuscular sclerosis, stem vessel endovasculopathy)

Range of features in distal villi:

- Avascular villi
- Villous stromal-vascular karyorrhexis (hemorrhagic endovasculitis)
- Delayed villous maturation (distal villous immaturity, placental maturation defect)

Clinical Context: There are a variety of maternal and fetal conditions that either directly or indirectly predispose to FVM (see Table 10.1). Umbilical conditions, some mediated by maternal or fetal disorders, also predispose to FVM (see Table 10.1). While placental patterns of FVM usually occur in the latter half of the third trimester, and therefore following gestational viability, on occasion they can be seen in second trimester gestations. FVM is a post-delivery diagnosis, and therefore per se is clinically silent, yet mothers can present with signs and symptoms reflecting decreased fetal movement. Likewise, there are a variety of antenatal, intrapartum, and postpartum signs

Table 10.1 Conditions predisposing to fetal vascular malperfusion

Maternal/intrauterine:
Oligohydramnios
Polyhydramnios
Diabetes mellitus (DM)
Abnormal uterine anatomy (e.g. bicornuate uterus)
Vasa previa
Multifetal gestation
Hypertensive and autoimmune conditions associated with maternal vascular malperfusion
Fetal:
Congenital cardiac defects
Diminished urinary output (intrinsic renal disorders, posterior urethral valves)
Leukocytosis, including transient myeloproliferative disorder in trisomy 21
Polycythemia (antenatal, prolonged)
Hyperglycemia (antenatal, prolonged)
Hereditary hypercoagulability (homozygous or compound heterozygous)
Umbilical cord conditions:
Abnormal cord insertion: velamentous, marginal, amnion web
Hypercoiling
True knot
Nuchal/body-wrapped cord
Long cord
Narrow cord diameter
Single umbilical artery
Marked cord edema (proposed)

Table 10.2 Fetal/neonatal clinical associations with fetal vascular malperfusion

Fetal growth restriction
Fetal macrosomia
Intrapartum nonreassuring fetal heart tones
Meconium
Low Apgar scores
Birth asphyxia
Early onset seizures
Stroke
Permanent neurodisability
Normoblastemia
Refractory hypoglycemia
Neonatal thrombocytopenia
Stillbirth

Table 10.3 Fetal vascular malperfusion: Grading and specific considerations

Grading:

1) High grade:
   a. > 45 avascular villi in 3 disc sections (15 avascular villi/section); or
   b 2+ occlusive/nonocclusive thrombi in chorionic +/- stem villi; or
   c Multiple (3+) nonocclusive thrombi

Specific considerations:

1) Intramural fibrin deposition:
   a. Focal: 1/slide
   b. Recent: Subendothelial/intramural
   c. Remote: Calcified
2) Avascular villi:
   a. Small foci: 3+ foci of 2-4 avascular villi/focus
   b. Intermediate foci: 3+ foci of 5-10 avascular villi/focus
   c. Large foci: 3+ foci of 10+ avascular villi/focus
3) Villous stromal-vascular karyorrhexis:
   a. 3+ foci of 2-4 terminal villi showing karyorrhexis of fetal cells with preservation of surrounding trophoblast

and symptoms associated with FVM and its untoward effects on fetal/neonatal well-being (see Table 10.2).

Proposed Pathogenesis: The etiology is usually at the umbilical cord level due to conditions that lead to physical constraint of normal umbilical vascular flow[1–7]. Other etiologies include fetal somatic disorders resulting in diminished somatic arterial outflow, or to conditions that render the fetal blood hyperviscous. Two generalized patterns of downstream fetal flow restriction have been recognized conceptually: *segmental/complete* and *global/partial*[8]. These patterns are addressed later in the chapter, with the caveat that causes and resultant microscopic features overlap. Of note, high-grade patterns with an increased predictive risk of untoward outcome[8–10] are addressed in Table 10.3, and in Chapters 33 and 34. Definitions of high risk patterns for individual gross and microscopic FVM findings are included in relevant sections to follow.

Ancillary Testing: Rarely is post-delivery testing with respect to etiology of value, though interrogating fetal/neonatal/parental hypercoagulability can be considered if an alternative predisposing condition to FVM is not identified.

Gross Features (By Location): *Umbilical cord*: A number of gross abnormalities can be seen, as outlined in Table 10.1. Some are self-explanatory, but several merit specific mention. A velamentous (membranous) insertion refers to termination of the umbilical cord within the extraplacental membranes, including between lobes of multilobate placentas (Chapter 16; Figure 10.1). A marginal (battledore) umbilical insertion occurs on the chorionic plate, but at or within 1 cm of the disc periphery (Figure 10.2). An amnion web tethers the umbilical cord to the chorionic plate such that the chorionic vessels splay at abnormally acute angles. Hypercoiling, by definition, refers to > 3 coils/10 cm[11]; however, a good visual rule of thumb is when two noncontiguous outer edges of Wharton's jelly come into contact at the coil (Figure 10.3). Hypercoiling may be diffuse or regional along the cord length. Furthermore, there are different patterns of coiling, listed here in descending frequency: rope, undulating, segmental, and linked. Hypercoiling is among the commonest of cord abnormalities[12,13] – particularly the segmented and linked patterns[7] – correlated with fetal/neonatal complications of FVM. At term, a long cord umbilical cord is variably defined as > 70 to > 80 cm[14]. Long umbilical cords are also associated with true knots, hypercoiling, and nuchal/body cords[15]. At term, a narrow umbilical cord (below the tenth percentile) is technically defined as <

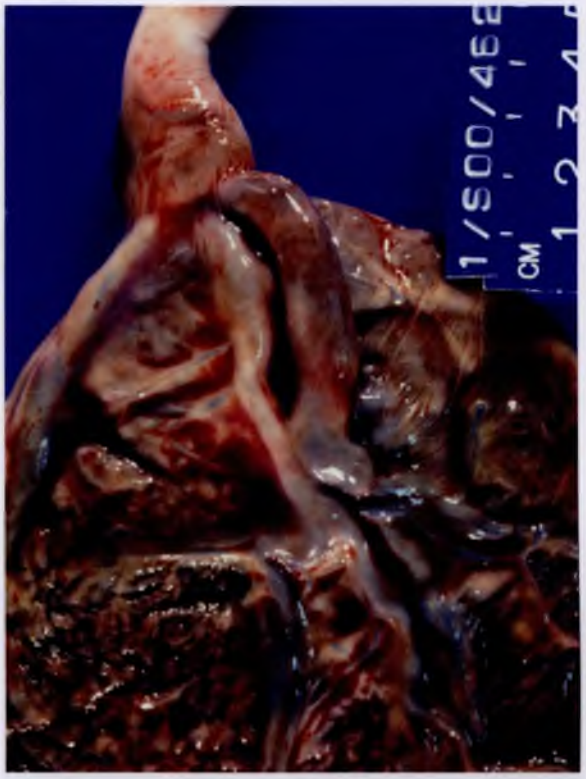

Figure 10.1 Velamentous cord insertion with chorionic vascular ectasia and thrombosis.

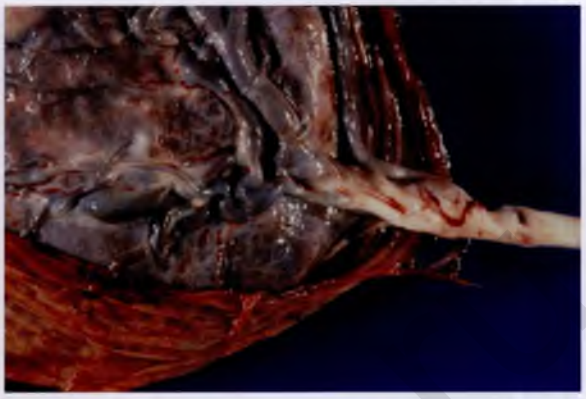

Figure 10.2 Marginal cord insertion with chorionic vascular ectasia and thrombosis.

Figure 10.4 Flat cord area near placental insertion due to tight ankle wrapping (see Figure 10.5).

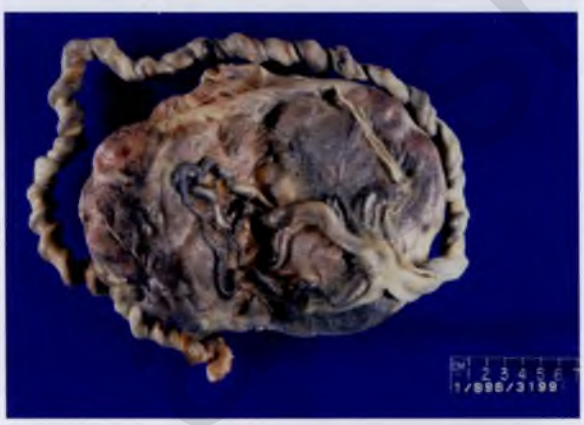

Figure 10.3 Hypercoiled umbilical cord with chorionic vascular ectasia and thrombosis.

0.8 cm in diameter[16], although in practice cords < 1.0 cm are likely at risk for vascular compromise. Umbilical cord edema (> 2.0 cm), conversely, may also predispose to vascular flow compromise, though good data for this association is lacking. As for additional gross cord abnormalities, there may be a flat umbilical cord, appearing ovoid rather than round on cross section, often with compression of Wharton's jelly (Figures 10.4 and 10.5). The umbilical vein can be ectatic, appearing notably dilated on visual inspection. Rarely is umbilical vein thrombosis visualized, having a globally engorged, spiraled appearance; and on palpation in the fresh state, contains, immobile blood.

Placental muscular vessels – Chorionic and stem villi: Chorionic vessels can exhibit a range of features reflecting restricted venous outflow, from recent to remote with respect to delivery. The earliest discernible gross finding is vascular ectasia, defined as a chorionic vessel at least four times the caliber of its neighbors (Figure 10.6)[17]. Next in evolution is recent thrombosis, manifest in the fresh state by distended vessels containing blood that is no longer freely movable on palpation. Thrombus organization exhibits visible off-white linear strands of fibromyxoid intimal proliferation in still-distended vessels (Figure 10.7),

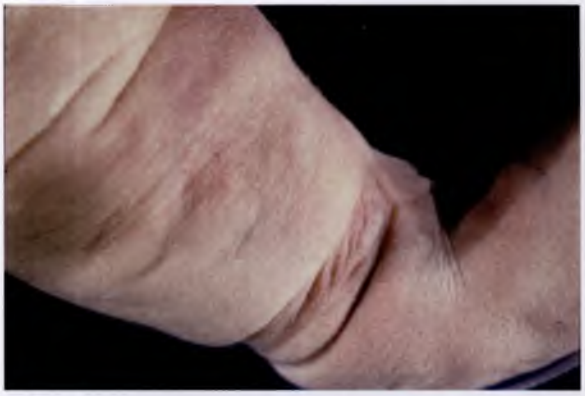

Figure 10.5 Term fetal death; tightly wrapped lower leg cord, as noted by cutaneous indentation.

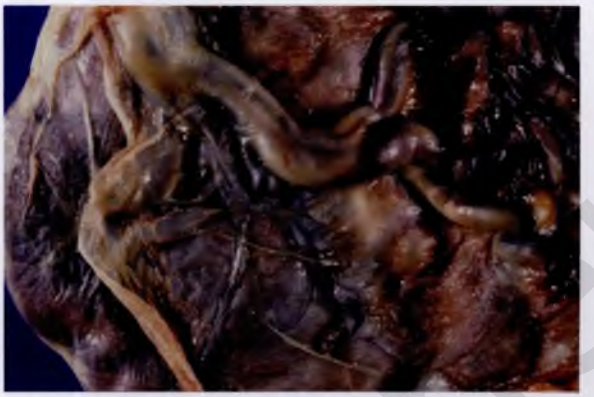

Figure 10.7 Chorionic vascular ectasia and organizing thrombosis, as evidenced by linear streaks of fibromyxoid intimal proliferation.

Figure 10.6 Chorionic vascular ectasia due to recent thrombosis; note caliber of central vessels, dilated at least 4 times that of adjacent nondistended counterparts.

Figure 10.8 Remote chorionic thrombosis, present inferior to cord insertion, with luminal ablation and calcification.

culminating over time in remote thrombosis. This latter finding is uncommon, but when present, vessel caliber is diminished by luminal obliteration, containing chalky white streaks of dystrophic calcification (Figure 10.8). On cut surface, affected vessels may show ectasia with or without linear intraluminal lamination typical of organizing thrombi (Figure 10.9), or complete luminal ablation with remote thrombosis (Figure 10.8). For practical purposes, stem villi do not demonstrate visible features of FVM grossly.

Capillary vessels – Distal mature intermediate villi terminal villi: On rare occasion a region of avascular villi is large enough to be visible as a discrete, angulated, firm off-white lesion on cut surface (Figure 10.10).

Microscopic features (by location):

Umbilical cord: Despite that the etiology of flow restriction is usually present at the umbilical cord level, microscopic changes are rare within the cord. Thrombosis can be present, with features identical to that described for chorionic and stem vessels below. Also uncommon are changes that reflect mural ischemic damage, including myocyte devitalization (loss of nuclear staining) and vasculitis, in this setting a noninfectious fetal inflammatory response to damaged tissue.

Placental muscular vessels – Chorionic and stem villi: Microscopic ectasia follows the rule of four – at least four times the caliber of similar-sized vessels[17] (Figure 10.11). In addition to ectasia, recent thrombi demonstrate loss of endothelial integrity, extravasation of red cells into the inner luminal wall, and adherent luminal fibrin. Organizing thrombi exhibit luminal fibrin incorporation by fibro-intimal proliferation to form a neo-intima (Figure 10.12). Organized thrombi are histologically indistinguishable from intramural

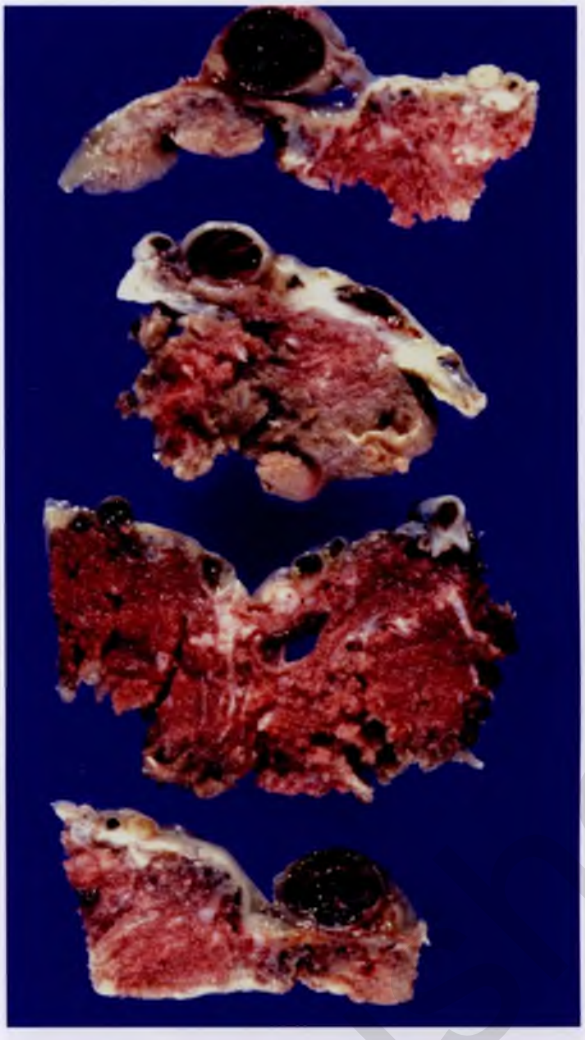

Figure 10.9 Recent chorionic vascular ectasia and thrombosis on cut surface, with marked dilatation compared to unaffected and indistinct counterparts; some vessels exhibit fibrin lamination.

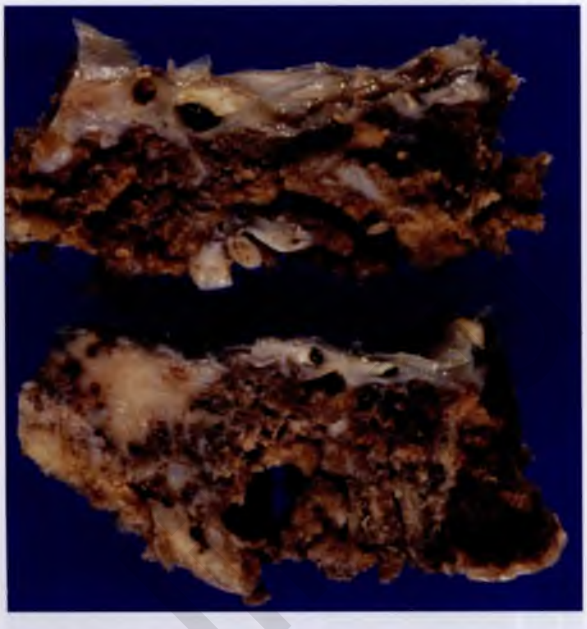

Figure 10.10 Remote chorionic thrombosis with incomplete luminal obliteration by calcified fibrin; note the wedge-shaped zone of avascular villi (lower cross section, on the left).

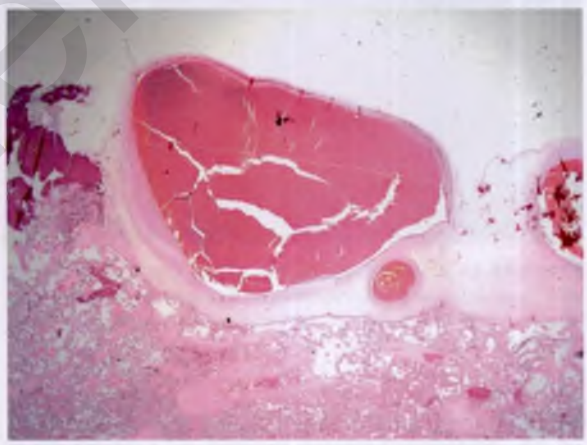

Figure 10.11 Chorionic vascular ectasia and organizing thrombosis (lower left luminal quadrant); note caliber of affected vessel, dilated at least 4 times that of adjacent nondistended counterparts.

fibrin deposition (synonym: intimal cushion), containing mural fibrin invested by a fibrous neo-intima (Figure 10.13)[18]. Intramural fibrin deposition is the result of endothelial damage and repair within placental muscular fetal vessels; this pattern can result either from incorporated thrombosis, as noted, or from non-thrombotic forms of endothelial injury such as flow turbulence or direct mechanical trauma. Remote thrombi, as with remote intramural fibrin deposition, contain intramural dystrophic calcification, embedded in the neo-intimal fibrous wall (Figures 10.14 and 10.15). Stem vessels, located downstream of more proximal thrombi, show stem villous obliteration (synonyms: fibromuscular sclerosis, stem vessel endovasculopathy), the by-product of flow cessation in affected vessels. Histologically this feature is manifest by progressive luminal fibroblastic ingrowth (Figures 10.16 and 10.17); in early phases, there is loss of endothelial integrity, followed by progressive intramural red cell extravasation and fragmentation (Figure 10.18). Hemosiderin may be seen. Stem villous

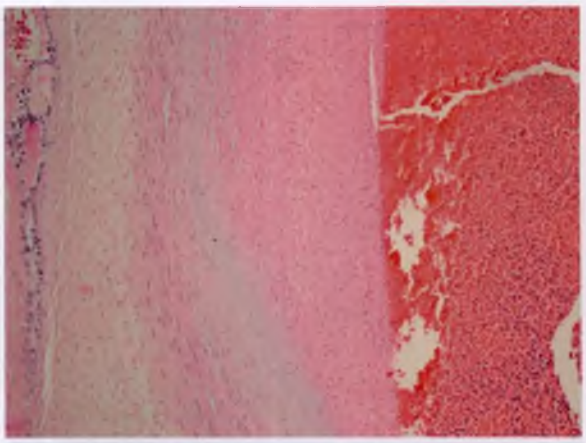

Figure 10.12 Higher magnification of Figure 10.11; adherent fibrin incorporation into a neo-intima (intimal cushion).

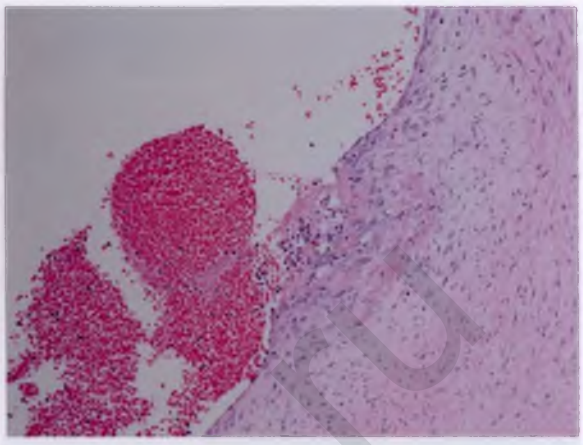

Figure 10.13 Stem vessel intimal cushion; the luminal organizing fibrin indicates this is secondary to thrombosis, otherwise the intramural fibrin could be the result of nonthrombotic endothelial damage and repair.

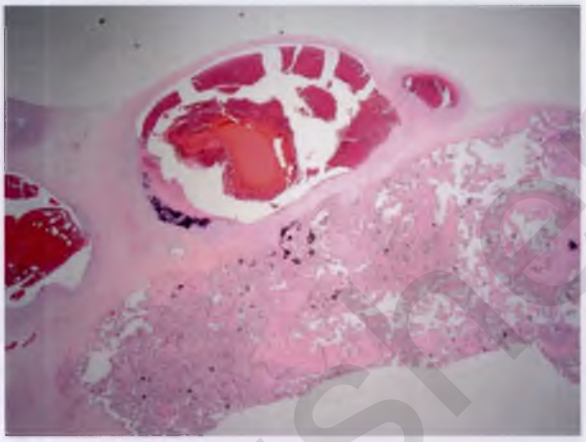

Figure 10.14 Chorionic vascular ectasia and remote thrombosis with mural calcification (lower left luminal quadrant); note caliber of affected vessel, dilated at least 4 times that of adjacent nondistended counterparts.

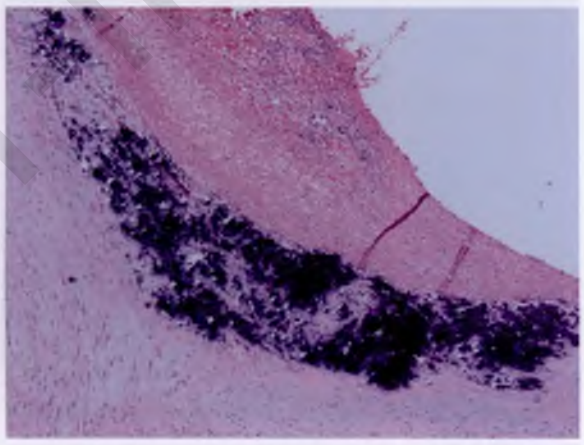

Figure 10.15 Higher magnification of Figure 10.14; adherent fibrin incorporation into a neo-intima (intimal cushion), which exhibits dystrophic calcification.

obliteration is the histologic analog in muscular fetal vessels to downstream capillary-level villous stromal-vascular karyorrhexis (see below). Within stem villi, this process culminates over time in fully avascular stem vessels. (Figure 10.19). Pitfalls in diagnosis with advanced stem villous obliteration include tangential sectioning and prolonged intrauterine demise. Densely eosinophilic ropy collagen within fibro-intimal proliferation can be misinterpreted as fibrin, and therefore mistaken for intramural fibrin deposition.

Capillary vessels – Distal mature intermediate villi terminal villi: Following cessation of blood flow into downstream villi, villous stromal-vascular karyorrhexis (synonym: hemorrhagic endovasculitis) evolves, manifest as capillary disintegration (endothelial karyorrhexis and loss of integrity) with subsequent red cell extravasation and fragmentation into the villous stroma (Figures 10.20 and 10.21)[10]. Stromal karyorrhexis and hemosiderin can be seen. As the interval between loss of flow and delivery widens, there is progressive disappearance of red cells and nuclear debris, culminating in the end-stage pattern of collagenized avascular villi (Figure 10.22). The earliest microscopically detectable feature, capillary disintegration, likely begins within many hours of flow cessation. Established villous stromal-vascular karyorrhexis takes days to evolve,

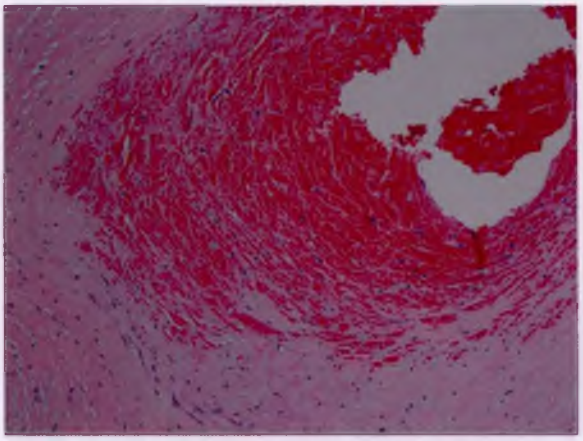

Figure 10.16 Stem villous obliteration, early intermediate stage, with loss of endothelial integrity, erythrocyte extravasation, and fibroblast ingrowth.

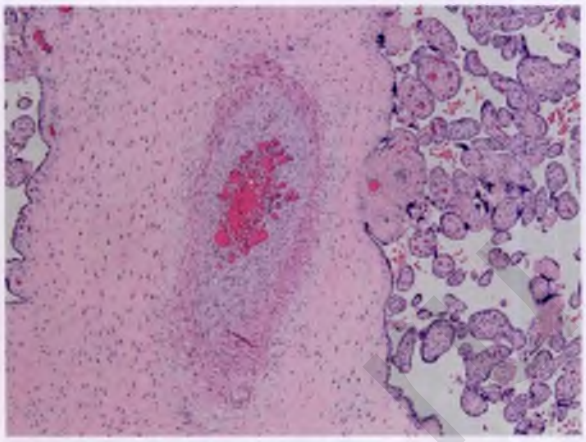

Figure 10.17 Stem villous obliteration, later intermediate stage, with fibroblast ingrowth and luminal septation.

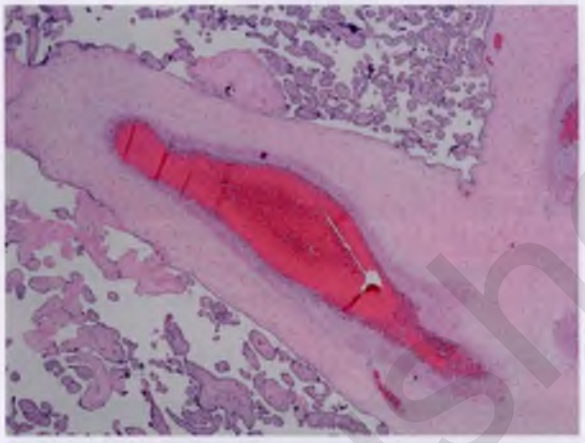

Figure 10.18 Stem villous obliteration, recent, secondary to upstream vascular obstruction, with ectasia, loss of endothelial integrity, and early erythrocyte extravasation (e.g., lower right).

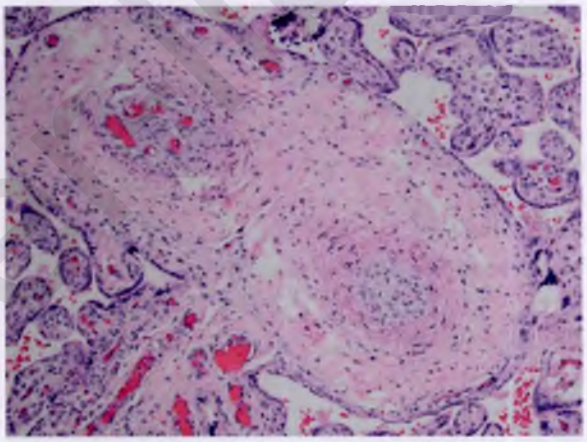

Figure 10.19 Stem villous obliteration, late intermediate stage, with advanced fibroblast ingrowth and luminal septation (left) and complete luminal obliteration (right).

and avascular villi likely require at least a week, if not weeks. Once villi become fully avascular, there is no further evolution of microscopic changes[19]. Delayed villous maturation (synonyms: distal villous immaturity, placental maturation defect) refers to the microscopic pattern of enlarged distal villi for gestational age with scant syncytiotrophoblast rimming and centrally placed capillaries (Figure 10.23). This pattern, in the setting of FVM, reflects chronically reduced fetal blood flow velocity into affected downstream villi. Experimental evidence has demonstrated that adequate capillary flow is required for villous modelling into a mature phenotype, with capillaries that abut the villous trophoblast to form so-called vasculosyncytial membranes[20,21]. Delayed villous maturation can be subtle and somewhat subjective. A good rule of thumb for evaluating this feature is to look for intermixed avascular villi singly or in minute clusters, usually containing stromal nuclear debris (Figure 10.24). Avascular villi in this context likely reflect reduction in distal flow of sufficient extent to render lethal metabolic and hemodynamic capillary damage, with subsequent karyorrhexis and eventual dissolution. Pitfalls in the diagnosis of villous stromal-vascular karyorrhexis include acute intravillous hemorrhage, processing artifact (fetal red cells above the plane of tissue), and passive changes of recent intrauterine

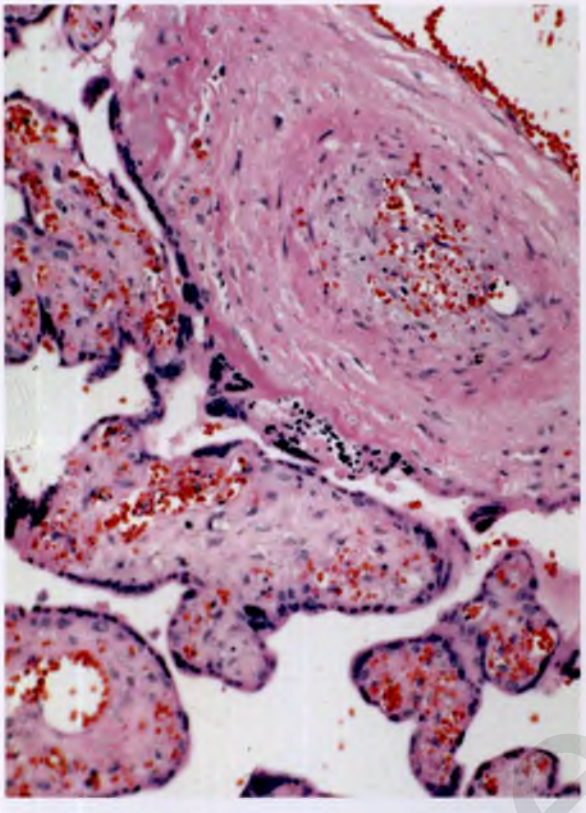

Figure 10.20 Villous stromal-vascular karyorrhexis in capillary vessels, with loss of endothelial integrity and erythrocyte extravasation and fragmentation; note stem vessel counterpart, stem villous obliteration.

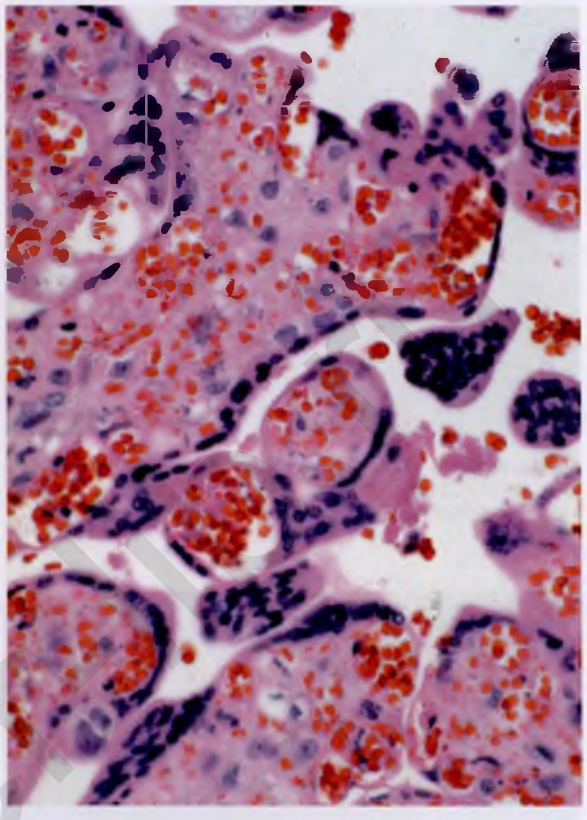

Figure 10.21 Villous stromal-vascular karyorrhexis in capillary vessels at high power, with loss of endothelial integrity and erythrocyte extravasation and fragmentation.

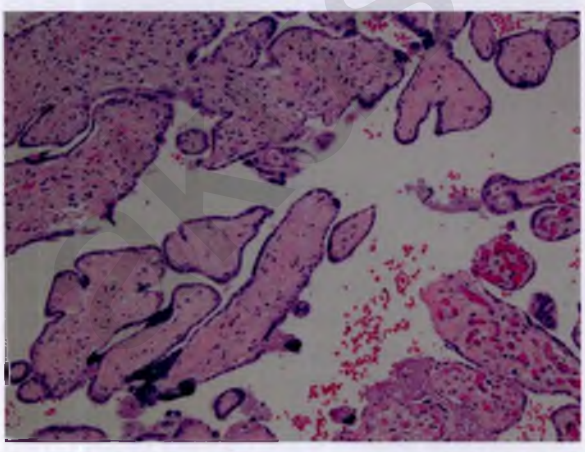

Figure 10.22 Avascular villi, central cluster, flanked by advanced villous stromal-vascular karyorrhexis (upper left) and delayed villous maturation (lower right).

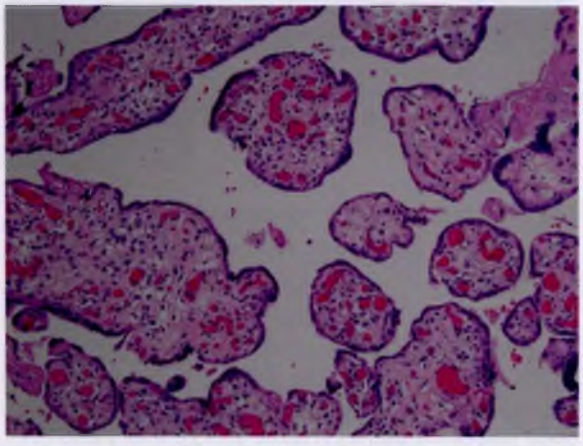

Figure 10.23 Delayed villous maturation, with enlarged relatively immature villi, diminished syncytial knots, and centrally placed capillaries. Note deficient vasculosyncytial membrane formation, evidenced by stromal interposition between capillaries and perimeter trophoblasts.

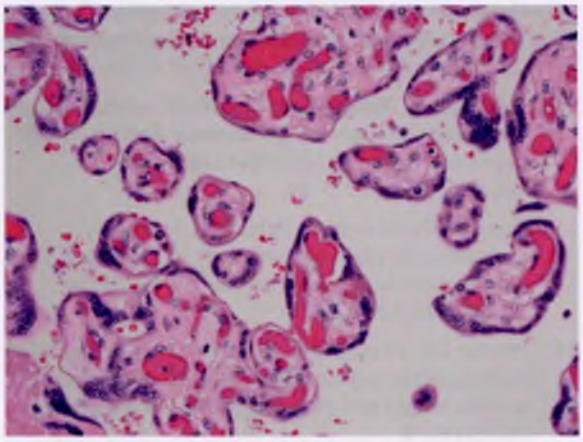

Figure 10.24 Delayed villous maturation, with enlarged relatively immature villi, diminished syncytial knots, and centrally placed capillaries. Note admixed fully avascular villi.

demise due to other etiologies. Avascular villi can be seen with senescent chronic villitis, in which case the acellular stroma appears more hyalizined than collagenized. With prolonged intrauterine demise, distal villi become globally avascular. Delayed villous maturation has overlap features with chorangiosis, in so far as villi are enlarged and relatively immature-appearing. However, hypervasculity is not present in the former, whereas central capillaries and nuclear debris are not seen in the latter.

Patterns of Fetal Vascular Malperfusion

As previously stated, the following dichotomous scheme refers to patterns of downstream effects that arise from all manner of placental fetal blood flow restriction. The construct is conceptual, and as such does not fully discriminate etiologic mechanisms that give rise to distinct downstream patterns. Thus, one mechanism may give rise to overlap findings that include both segmental/complete and global/partial patterns in a given placenta.

Segmental FVM (Complete Obstruction)[8]

Definition and Presumptive Cause: Thrombotic occlusion of chorionic or stem villous vessels, or stem vessel obliteration; often, but not always, related to targeted umbilical cord compromise/critical stasis. The distribution of the lesions is segmental, therefore the thrombus or obstruction results in complete flow cessation to downstream villi. Effects in muscular (chorionic, stem) fetal veins include large vessel thrombi, intramural fibrin deposition (in this setting presumptively due to organized thrombosis), and stem villous obliteration. Capillary vessels (distal mature intermediate and terminal chorionic villi) exhibit intermediate (5–10 villi/focus) and large (>10 villi/focus) clusters of avascular villi/villous stromal vascular karyorrhexis; see Table 10.3 for grading.

Global FVM (Partial or Intermittent Obstruction)[8]

Definition and Presumptive Cause: Partially obstructed umbilical blood flow; usually but not always related to predisposing umbilical cord lesions. The obstruction is partial or intermittent, and the lesions are distributed over much of the placenta. Effects in muscular (chorionic, stem) fetal veins include vascular ectasia and intramural fibrin deposition (in this setting presumptively reflecting endothelial damage by altered flow rather than thrombosis *per se*). Capillary vessels (distal mature intermediate and terminal chorionic villi) contain small foci of avascular villi/villous stromal vascular karyorrhexis (2–4 villi/focus); see Table 10.3 for grading. Regional or near global delayed villous maturation can also be seen.

Prognostic Implications: Features of FVM, either global or segmental, are seen in up to 6.4 percent of all placentas sent for pathologic evaluation[9,22,23]. However, the clinical significance ranges dramatically, from incidental if findings are scant, to catastrophic if FVM is prolonged/severe, with a risk for stillbirth (Chapter 33)[4,6,7,24,25], various forms of neurodisability in live births, including stroke, (Chapter 34)[9,26–30], and other visceral thrombosis[26,31]. As a general principle of this and many other placental disorders, the more advanced/severe the process, the greater the likelihood for untoward fetal/neonatal outcome.

Knowledge Gaps: Clinically, literature and practice lack antenatal ascertainment of FVM in specific, much less *a priori* discernment of potential fetal/neonatal outcome. Antenatal practice relies on standard measures of fetal well-being, as with any/all other intrauterine conditions. Antenatal recognition is bounded on two sides: the typical silent course of FVM, and when evident, intrapartum fetal distress without identification of predisposing cause.

Pathologically, current research is targeted toward identification of placental FVM patterns deemed "high grade," and therefore at increased risk of untoward outcome in live births.

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Chapter 11

Loss of Fetal Vascular Integrity

Drucilla J. Roberts

Loss of fetal vascular integrity results in hemorrhage or villous edema. Fetal hemorrhage can be catastrophic from vascular disruption (as in vasa previa) or relatively mild (as in intervillous thrombi). Fetal hemorrhages are common and usually benign. We know this because of various diagnostic modalities showing low levels of fetal cells or DNA within the maternal blood of essentially all pregnancies. Yet, occasionally and often without any clinical risk factors, massive fetal bleeding occurs and results in significant fetal compromise or death. Unfortunately, most of these events are random and idiopathic with no possible treatment other than emergent delivery. Most fetal hemorrhages are slowly progressive, but rapid acute hemorrhages can occur.

Villous edema results when there are leaky villous capillaries with increased hydrostatic pressure from venous obstruction or decreased oncotic pressure from, for example, severe fetal liver disease. Most villous edema is focal and inconsequential. Clinically significant villous edema is either patchy or diffuse with or without accompanying hydrops fetalis. Edema is also common in early pregnancy failures as a consequence of absence of a functioning fetal vasculature (see Chapter 2).

HEMORRHAGE

Intervillous Thrombi (IVT)

Definition: *Intervillous thrombi*, often laminated, are space-occupying lesions in the intervillous space without significant "collateral damage" to adjacent villi or trophoblast

Clinical Context: Intervillous thrombi are relatively common placental findings and typically occur without a significant clinical history. They are thought to be due to small volumes of fetal-maternal hemorrhage[1]. They are more frequent in pregnancies complicated by blood group incompatibilities (anecdotal experience). Recently they have been seen more commonly in pregnancies with maternal diabetes[2], although this might be confounded by hypertension. They have also been reported to be more frequent in pregnancies complicated by maternal obesity[3], placentas from white women[4], intrauterine growth restriction[5,6], hypercoiled umbilical cords[7], and male gender[8].

Proposed Pathogenesis: Trophoblast disruption leads to loss of fetal vascular integrity and fetal hemorrhage, usually focal and of small volume. Maternal hemostatic mechanisms are believed to rapidly "clot off" the hemorrhage in most cases. Fetal hemoglobin can be found in the center of IVT by immunohistochemistry[1,2] The origin of the trophoblastic damage is unclear. It may be due to apoptosis, shearing forces, or ischemia[2].

Gross Features: IVT present as mass lesions in the parenchyma that are either red, "currant jelly"-like or pink/tan fibrin-like. They typically have grossly visible laminations (Figure 11.1a) and should be in the center of the parenchyma. If they are restricted to the subchorionic region, they are subchorionic thrombi and may represent a different etiology (see Chapter 18). IVT are usually in the range of 0.5–2 cm in greatest dimension and are usually irregular in shape.

Microscopic Features: IVT are space-occupying lesions in which a laminated irregularly shaped area of clotted blood ("thrombus") is present in the maternal space, pushing the villi "away," usually without much associated villous damage (Figure 11.1b). IVT are usually composed of only red blood cells and fibrin, but in some IVT, there are prominent inflammatory cells and cellular debris (Figure 11.1c). Occasionally, the immediate surrounding villi are encased in fibrin and show necrosis. IVT only occur in the intervillous space. Thrombi within placental septa can look very similar to IVT, except for their location (Figure 11.2). Septal fluid has been shown to be thrombogenic[9], and thrombi that form within the septa may have a different etiology; they have not been studied for presence of fetal hemoglobin.

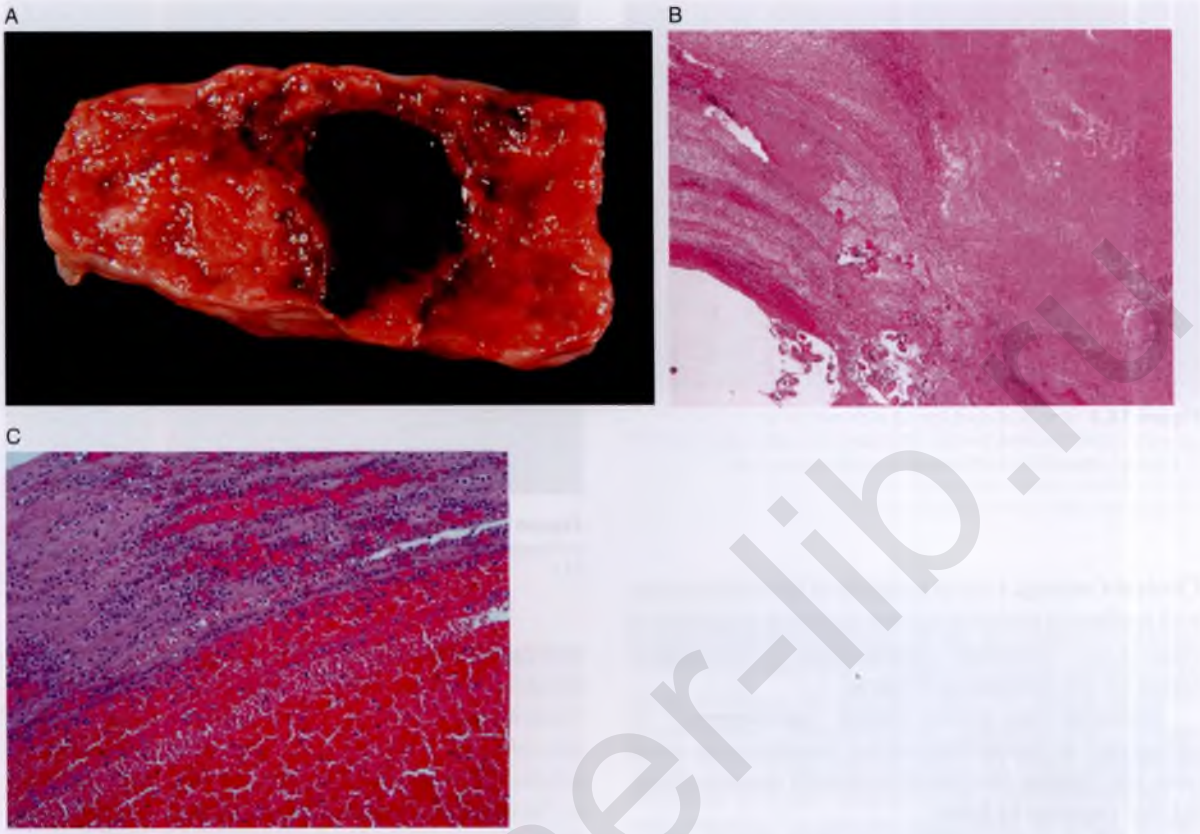

Figure 11.1 (a) Intervillous thrombus (gross). (b) Intervillous thrombus. Notice the paucity of pathology in surrounding placenta. (c) Inflammatory cells within an intervillous thrombus. Images provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

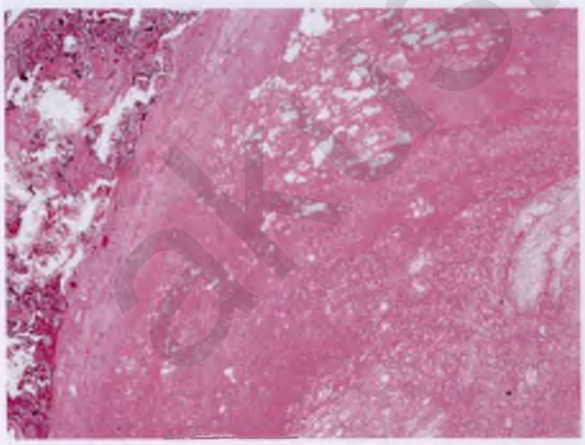

Figure 11.2 Septal hemorrhage/thrombus.

Ancillary Testing: No ancillary tests are necessary for the diagnosis of IVT. Immunohistochemistry for hemoglobin F can be confirmatory for pathogenesis.

Prognostic Implications: IVT seem to be innocuous pathologies without any clinically relevant associations. As they probably represent minute fetal-maternal hemorrhages, multiple intervillous thrombi may be more significant than the usual one[10], but in our experience, they have no consistent clinical significance.

Knowledge Gaps: The true pathogenesis of IVT remain unexplained. What causes small fetal-maternal hemorrhages? Although we hypothesize that it must be due to trophoblastic damage, this has not been demonstrated. The increased incidence seen in placentas from diabetic mothers is perplexing and may be due to increased trophoblastic apoptosis. A relationship to blood group incompatibilities may exist, but this has not been proven[11].

Fetal Vascular Tears, Ruptured Vasa Previa

Definition: Large vessel(s) with disruption of the vascular wall leading to fetal hemorrhage.

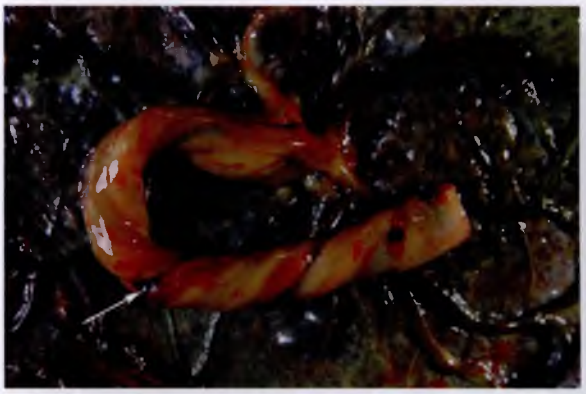

Figure 11.3 Umbilical cord (gross) with meconium related ulcerations (white arrow). Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

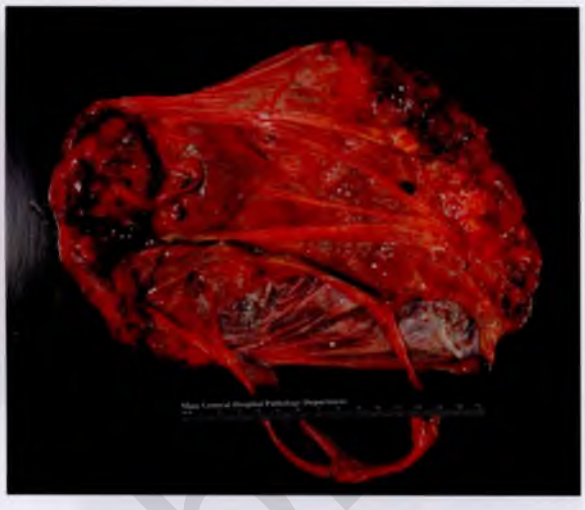

Figure 11.4 Lethal ruptured vasa previa (left). Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

Clinical Context: Loss of integrity of the fetal vascular wall leading to hemorrhage can occur for a number of reasons (see "Proposed Pathogenesis"). Two clinical scenarios are summarized below:

Ruptured vasa previa (either "spontaneous" or iatrogenic) or rupture/tear of any membranous vessel (also see Chapter 16): can present with massive bleeding per vaginam in labor.

Umbilical cord vascular tears, often due to meconium myonecrosis (also see Chapters 16 and 19): can present with fetal compromise including death or rarely with bleeding per vaginam in the context of ruptured membranes. Umbilical cord vascular tears can also lead to umbilical hematomas/hemorrhage contained in Wharton's jelly. These are rare and fatal complications of vascular injury (see Chapter 16). They almost universally present with fetal death.

Proposed Pathogenesis: In vasa previa the vessels at the cervical os can rupture following spontaneous rupture of membranes or iatrogenically with artificial rupture of membranes. In our experience, the vessels that rupture are often damaged and therefore weakened by other insults, including focal necrosis due to pressure from the presenting part, toxic necrosis from prolonged meconium exposure, or inflammatory injury due to fetal inflammation. Ulceration as a rare complication of meconium myonecrosis is one cause of umbilical cord vascular tears[12] (see Chapter 16 and Figure 11.3). Meconium is thought to be toxic to vascular muscle, leading to apoptotic-like myonecrosis that decreases vascular integrity. Any pathology that weakens the umbilical vascular wall can result in tears that can be either "revealed" – bleeding into the amniotic cavity then per vaginam with membrane rupture or "concealed" – forming a hematoma contained within the cord. The resulting cause of fetal death depends on whether the rupture is "revealed" – death due to anemia or "concealed" – death due to obstruction of the umbilical vein secondary to the pressure of the hematoma.

Gross Features: Ruptured vasa previa (or rupture of membranous fetal vessels not overlying the cervical os) can be identified by gross dissection of the vascular structures (Figure 11.4). Usually the involved vessel(s) are transected and easily identified. In some cases there is tearing but incomplete transection of the vessel, which can be difficult to identify without a thrombus or adjacent membranous hemorrhage. Classically, ruptured vasa previa is due to membranous insertion of the umbilical cord, but cases may involve other membranous vessels (e.g. bridging vessels between bilobate placentas or accessory lobes and "wandering" membranous vessels in marginal or peripheral insertion of the umbilical cord) that are damaged by virtue of overlaying the cervical os during labor or by prolonged/severe inflammation or meconium. Umbilical cord tears are grossly identified by exposed vessels (Figure 11.4), which are especially frequent when there is meconium myonecrosis with associated loss of Wharton's jelly and necrosis of the amniotic epithelium on the umbilical cord (also see Chapter 16). Umbilical hematomas present with massive dilatation of the umbilical cord due to

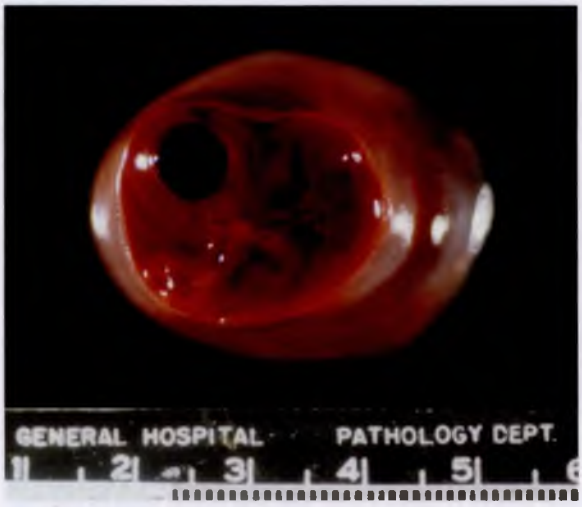

Figure 11.5 Umbilical cord hematoma resulting in stillbirth. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

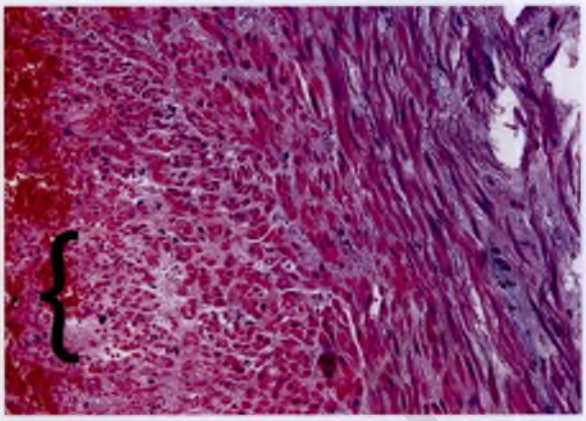

Figure 11.6 Focal umbilical cord vascular wall necrosis (highlighted with {) in a term stillbirth, presumably due to cord occlusion secondary to pressure obstruction. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

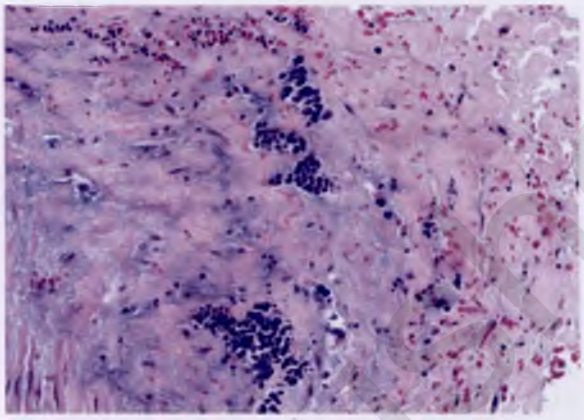

Figure 11.7 Umbilical cord with chronic hemorrhage and lethal hematoma showing extramedullary hematopoiesis in Wharton's jelly. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

hemorrhage. These lesions are not subtle, and the umbilical cord is usually thick and firm, like a sausage (Figure 11.5), often with extension for many centimeters of its length. This should not be confused with the common cord insertional hemorrhage or perivascular hemorrhages due to iatrogenic traction of the umbilical cord at delivery of the placenta. These hemorrhages are small, contained, and usually perivascular and clinically insignificant.

Microscopic Features: Ruptured or torn fetal vessels can lead to massive acute and often fatal hemorrhage. Due to the acuteness of the lesion, there are often no histopathologic findings. In our experience, sections of the vessel taken at or near the rupture point often show evidence of damage, such as mural thrombi, hemosiderin, inflammation, apoptotic-like changes (as in meconium myonecrosis), or zonal coagulative muscular necrosis (Figure 11.6). The hemorrhage, if any remains, is poorly organized. If there is any chronicity to the hemorrhage (e.g. with slow leaks due to small tears), one may see evidence of fetal anemia with circulating erythroblasts or even extramedullary hematopoiesis (Figure 11.7). Umbilical cord vascular tears that result in cord hematomas show fresh hemorrhage dissecting within Wharton's jelly. Occasionally, with chronicity, there can be fibrin, hemosiderin, and evidence of fetal anemia with presence of immature erythroid precursors.

Ancillary Testing: No ancillary testing is useful.

Prognostic Implications: Rupture or tears of large fetal vessels are often lethal. If not, they can result in extreme hypovolemia or anemia, and their attendant complications.

Knowledge Gaps: None.

Intravillous Hemorrhage (Villous Stromal Hemorrhage, Chorionic Villous Hemorrhage)

Definition: "Free" blood in villous stroma, outside of blood vessels. Villi are filled with blood, not just focal

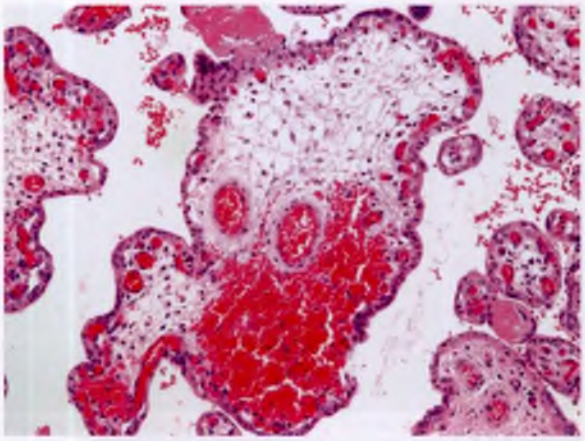

Figure 11.8 Intravillous (stromal) hemorrhage in a case of massive acute abruption.

hemorrhage (Figure 11.8)[13]. Typically only distal villi are affected. This differs from villous stromal vascular karyorrhexis or stem villous obliteration (see Chapter 10), which also involves stem and intermediate villi and where red blood cells and red blood cell fragments are seen within the vessel lumen and wall[14].

Clinical Context: *Intravillous hemorrhage (IVH)* theoretically occurs whenever there is enough pressure in the villi to cause rupture of the villous capillaries. An alternative hypothesis is that IVH occurs with hypoxic necrosis of the villous vessels/endothelium, leading to loss of vascular integrity and stromal hemorrhage[13]. Often the clinical situation involves one of the following pathologies: acute abruption (see Chapter 8), venous outflow tract obstruction as in tight true knots of the umbilical cord or prolapse, vacuum extraction as in a dilatation and evacuation (D&E), or direct trauma as in blunt force uterine injury, uterine rupture, or difficult manual extraction of the placenta.

Proposed Pathogenesis: The etiologies proposed for IVH include vascular/endothelial damage due to hypoxia or sudden increased intravascular pressure due to outside forces (e.g. abruption), vascular obstruction (cord accident), physical forces (manual extraction), or vacuum pressure (D&E). It is typically considered a hyperacute phenomenon, happening immediately after the insult, although histologically it can persist over longer time periods. We have seen IVH present in clinically documented abruptions dating at least one week[49]. The finding is more pronounced and more common when it occurs in early gestations, likely due to the relatively fragile vessels and less compact villous stroma. Later gestational ages have "stronger" villous vascular walls and are less likely to demonstrate IVH with one of the inciting pathologies (first and second trimester cases are often florid, whereas term cases might be only focal).

Gross Features: The presence of the associated pathologies give rise to most of the gross features (as in abruption or tight obstructive true knots of the umbilical cord), but the affected parenchyma is often very red and congested[13].

Microscopic Features: The involved chorionic villi have a "bag of blood" morphology easily identified at low power (Figure 11.8). The red blood cells in the villi are intact without fragmentation. Usually the hemorrhage is composed only of red blood cells (no inflammatory cells). When associated with either acute abruption or manual extraction, the IVH is usually adjacent to the basal plate or retroplacental hematoma (RPH) if present[13], but we have seen patches of IVH away from the RPH in many cases. When associated with venous outflow obstruction, the IVH is typically patchy throughout the parenchyma. Vacuum-associated IVH is often diffuse. The surrounding villi may show chorangiosis (see Chapter 9), congestion, and/or acute villous edema[13] (see below).

Ancillary Testing: Not useful.

Prognostic Implications: Prognosis for IVH follows its etiology; it is often poor due to severe hypoxia when associated with acute abruption and cord occlusion. Cases associated with manual extraction may show the pathologies that necessitated the procedure, for example, placenta accreta (see Chapter 28), retained placenta, or Asherman's syndrome[15]. One preliminary study found that IVH was associated with increased neonatal mortality in preterm infants[16].

Knowledge Gaps: The precise timing of IVH in relation to the insult is unknown. In our study we saw IVH in approximately 35 percent of documented "revealed" acute abruptions and these occurred from minutes to hours of the documented clinical abruption[49]. The timing of IVH onset associated with venous outflow obstruction is unknown. The variation due to gestational age has not been rigorously studied and may play an important role in the prevalence of IVH when due to any of the associated insults.

EDEMA

Edema of the placenta can involve the villi, membranes, and umbilical cord. It is debated whether edema is a cause or consequence of fetal hypoxia, but the association is robust. Specifically, studies have shown the need for newborn resuscitation with low cord-blood pH values[17], increased risk of neonatal deaths in prematurity[16], and development of neurodisability[18] in cases of significant acute villous edema. In this section, we illustrate three distinct patterns of villous edema: hydrops placentalis (all villi), diffuse villous edema (of immature intermediate villi), and patchy villous edema (of terminal villi).

Hydrops Placentalis (Villous Hydrops, Chronic Villous Edema)

Definition: Severe chronic edema in the villi and umbilical cord, immature villi, and a heavy placenta by weight are characteristics of hydrops placentalis.

Figure 11.9 Hydrops placentalis in a case of chronic fetal maternal hemorrhage at 29 weeks gestational age.

Clinical context: The etiology of *hydrops placentalis* is diverse[19] and includes immune (see below) and nonimmune causes (e.g. congenital anomalies, chromosomal anomalies, twinning, fetal dysrhythmias, nonimmune anemias including chronic fetomaternal hemorrhage and parvoviral infection, infection, inborn errors of metabolism, and congenital neoplasia). Hydrops placentalis is usually associated with hydrops fetalis, which is defined by peripheral edema and fluid collections in at least two sites (e.g. pleural and ascites). Typically hydrops fetalis is diagnosed by an ultrasound examination performed for size greater than dates, nonreassuring fetal testing, or a known complication of pregnancy from the list above. Hydrops fetalis is divided into two major categories: immune and nonimmune. Immune hydrops is due to blood group incompatibilities with transfer of maternal antibodies to the fetus resulting in hemolysis, severe anemia, and erythroblastosis. Classically immune hydrops is due to Rh- disease[20], but this is currently a rare phenomenon with proper obstetric management of the Rh- mother. Now we see ABO incompatibilities and lesser antigen alloimmune hydrops at least as often as Rh- disease[21–23]. Nonimmune hydrops is much more common than immune hydrops. There is such a long list of possible etiologies, but most have in common heart failure leading to anasarca involving both fetus and placenta. The etiology can usually be determined by thorough investigation including evaluation for anomalies, karyotype, microbiologic analysis, Kleihauer-Betke testing, blood smear, and a complete pathological evaluation (placenta and autopsy, if stillbirth or neonatal death follows).

Proposed Pathogenesis: Although a final common pathway for hydrops may not apply to all cases, heart failure and resultant anasarca is the most frequent. Some etiologies of hydrops cannot be neatly packaged as heart failure, and Machin[19] has categorized 5 basic pathways leading to hydrops: cardiovascular, chromosomal, anemia, thoracic compression, and twinning.

Gross Features: Hydropic placentas are heavy, boggy, and pale (Figure 11.9). Depending on the etiology, one may see specific features, for example a large chorangioma or multiple parenchymal nodules associated with malignancy.

Microscopic Features: Large edematous and immature villi predominate (Figure 11.10). The etiology of the hydrops can sometimes be diagnosed by placental histopathology (for details see Table 11.1).

Prognostic Implications: The prognosis of hydrops is poor with a mortality rate greater than 50 percent, depending on the etiology[24] and gestational age[25]. Maternal morbidity associated with hydropic pregnancies include polyhydramnios, preterm labor,

Table 11.1 Placental pathologic findings in hydrops placentalis

1) Category of diagnosis[19,37]	Placental histopathologic correlate
Cardiovascular	
High output failure	Nothing specific
Malignancy	Neuroblastoma can be seen circulating in the fetal vasculature (see Chapter 22)
Neoplasm	Chorangioma, umbilical cord hemangiomas (see Chapter 16)
Chromosomal	
Triploidy	Partial molar villous histology (see Chapter 4)
Trisomy 21	Myeloproliferative disease (see hematologic category)
Twin pregnancy	
Twin-Twin transfusion syndrome	Monochorionic diamniotic placentation usually with features of chronicity (see Chapter 25)
Twin reversed arterial perfusion	Monochorionic diamniotic or monoamniotic placentation with large surface arterial to venous direct vascular anastomoses (see Chapter 25)
Hematologic	
Any anemia	Circulating erythroblasts, normal
	Dysplastic as in Congenital dyserythropoietic syndromes[38]
	Neoplastic as in leukemias[39,40] and transient abnormal myelopoiesis[41,42] (see Chapter 22)
Infectious (see Chapter 12)	Viral infections: Inclusions (Parvovirus, CMV, HSV[43,44])
	Spirochete: classic histologic findings in syphilis[45–47]
	Parasite: identification of the organism in the umbilical cord or amniocytes, toxoplasmosis[48]
Metabolic	Storage diseases can demonstrate foamy cytoplasmic distention of the syncytiotrophoblasts, Hofbauer cells, and amniotic epithelium (see Chapter 24)
Urinary	Findings of chronic severe oligohydramnios, may show amnion nodosum (see Chapter 21)

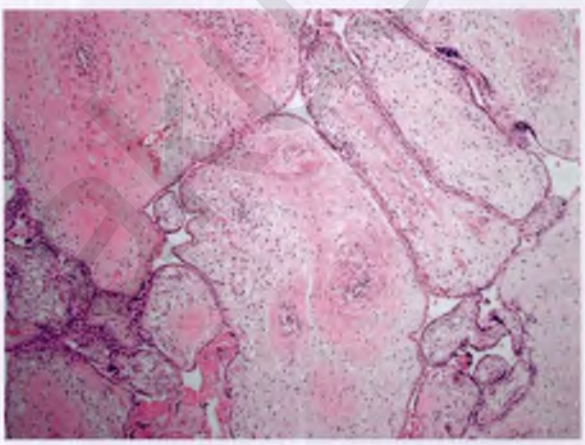

Figure 11.10 Histology of hydrops placentalis due to chronic anemia, from the placenta in Figure 11.9. Notice the large, immature-appearing edematous villi. There are numerous nucleated red blood cells in fetal circulation. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

hypertension, anemia, postpartum hemorrhage, birth trauma, gestational diabetes, and difficulty with delivery of the placenta[26]. An interesting but serious complication that can occur in mothers with hydropic gestations is termed "mirror syndrome." This phenomenon manifests as a maternal phenocopy of the fetal hydrops with development of peripheral edema, pulmonary edema, and, often, severe preeclampsia[27,28]. It has been reported postpartum[29], but most cases occur antepartum and resolve following delivery or with correction of the hydrops.

Knowledge Gaps: Although mechanisms have been proposed to explain the various pathways involved in generating the hydropic phenotype, not all are convincing. In all series of hydrops, there is always a percentage of cases (15–25 percent) in which the etiology remains unexplained[26]. With the

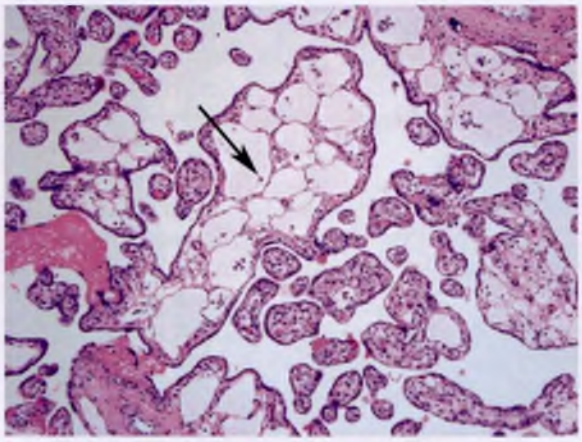

Figure 11.11 Diffuse villous edema with large "lymphatic-like" spaces and "floating" Hofbauer cells (arrow). Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

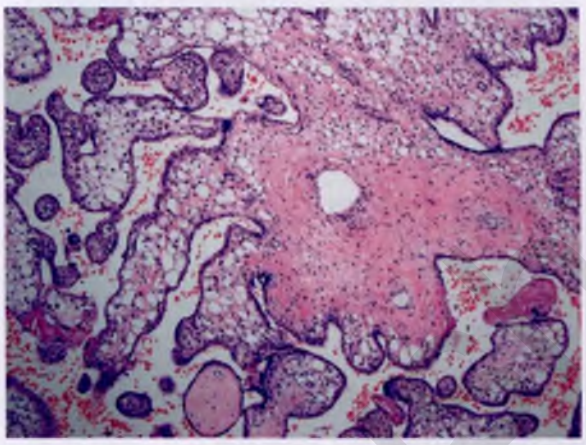

Figure 11.13 Diffuse villous edema of terminal and intermediate villi.

application of molecular testing, the number of idiopathic hydrops cases will likely decrease.

Diffuse Villous Edema (Patchy Edema, Immature Intermediate Villi)

Definition: Edematous stroma affecting primarily immature intermediate villi.

Clinical context: Most cases of *diffuse villous edema* occur in preterm deliveries with evidence of antenatal hypoxia (for example: low Apgar scores or need for resuscitation). It is associated with acute chorioamnionitis, neonatal death, and neurodisability[17,30,31].

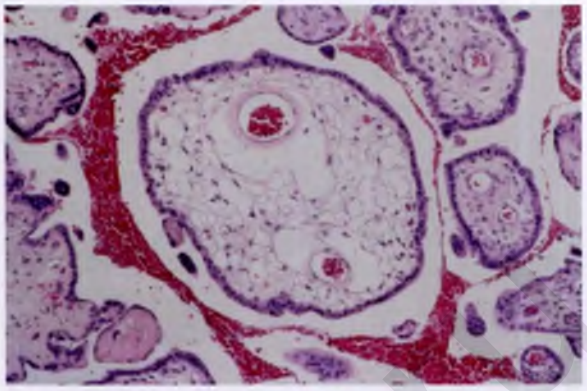

Figure 11.12 Diffuse villous edema with early cistern formation.

In our experience, many cases of diffuse villous edema follow a sentinel event, for example uterine rupture or complete placental abruption. A higher incidence of placenta previa has been noted with diffuse villous edema[17].

Proposed Pathogenesis: As is true for edema anywhere, increases in hydrostatic pressure from vascular compromise or decreased vascular oncotic pressure result in an abnormal transudate, causing increased extracellular fluid. In the placenta, the most common cause of increased hydrostatic pressure is fetal heart failure, usually from hypoxia. As the placenta has no lymphatics[32], the transudate fills the interstitial spaces in the loose villous stroma of immature intermediate villi and eventually causes breakdown between cells leading to the formation of spaces (often with "floating" Hofbauer cells, Figure 11.11) and later cisterns (Figure 11.12).

Gross Features: The placenta with diffuse villous edema generally is grossly normal. When severe, the placenta can be large, pale, and boggy (see above section on hydrops placentalis).

Microscopic Features: Diffuse villous edema involves primarily immature intermediate villi (Figure 11.13). The result is pale, clear villous stroma often with sharply edged "swiss cheese"-like spaces (Figure 11.11). The low-power look is of generalized pallor of the villi, and the high-power view shows the spaces. This should be differentiated from the normally pale villi of the immature state where the villous stroma is pale/clear, but without the sharply outlined spaces (i.e. is composed instead of a loose reticular stroma, Figure 11.14).

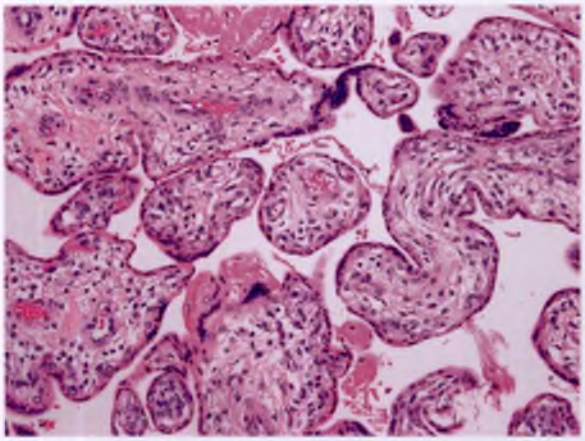

Figure 11.14 Normal immature villi. Notice absence of "swiss cheese"-like spaces in stroma.

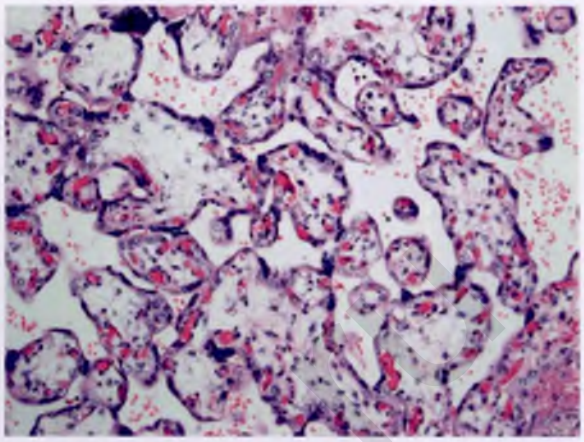

Figure 11.15 Patchy acute villous edema. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

Ancillary Testing: Not applicable.

Prognostic Implications: Diffuse villous edema has been associated with many neonatal morbidities and mortality in both preterm and term infants[16,30,31,33]. Morbidities include associations with cerebral palsy and other neurocognitive disorders and respiratory distress, as in hyaline membrane disease.

Knowledge Gaps: It remains somewhat controversial if villous edema is the cause or the sequela of a hypoxic insult. If increased hydrostatic pressure from vascular obstruction *causes* diffuse villous edema, then it should be a common finding with fetal vascular malperfusion (see Chapter 10), but this is not always the case. An attractive but unproven hypothesis is that compression of the villous vessels by the edema fluid may result in poor transfer of oxygen and nutrients from the maternal space to the fetal vessels or may compress the vessels increasing the work of the heart to perfuse the placenta[17].

Patchy Villous Edema of Terminal Villi

Definition: Villous stromal edema involving primarily terminal villi in a patchy distribution throughout the placenta. At least 15 percent of the distal villi must be involved[34].

Clinical context: This is a lesion that is often present focally, but when more than focal has been associated with fetal acidemia at term[34]. In this study by Avagliano et al.[34] placentas from low-risk term deliveries with unexpected cord blood pH < 7 were compared with placentas from term deliveries with normal cord pH and patchy acute villous edema was seen

Proposed Pathogenesis: This lesion is thought to be due to increased venous pressure leading to transudation of fluid into the interstitial space of the terminal villi. Abnormalities of cardiac function due to a subacute hypoxic insult is the proposed mechanism[34].

Gross Features: There are no specific gross features.

Microscopic Features: *Patchy villous edema* shows regions of distal/terminal villous expansion with pallor of the expanded stroma (Figure 11.15). The authors[34] make a distinction from the normal, somewhat reticular pattern of immature villi (Figure 11.14), but in my experience, vacuolar spaces in the terminal villi distinguish this pattern from villous immaturity.

Ancillary Testing: Not applicable.

Prognostic Implications: In the one report of this entity, term infants showed acidemia at birth[34]. Others have shown villous edema to be associated with high umbilical cord pH levels, although the type of villous edema was not illustrated[35]. Low cord pH has been associated with increased neonatal morbidity (seizures, hypoxic-ischemic encephalopathy, cerebral palsy, and cerebral hemorrhage) and mortality[36].

Knowledge Gaps: Mechanisms explaining the difference in pattern and prognosis between the various patterns of villous edema are unclear. If the pathogenesis is similar, one would expect the histopathology and prognosis to be as well. While well-defined and reproducible, these differences remain somewhat perplexing.

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Chapter 12

Placental Infections

Drucilla J. Roberts

Placental infections are rare but account for a large fraction of perinatal morbidity and mortality. Infectious pathology should be considered in cases of known or suspected maternal infection, intrauterine growth restriction (IUGR), hydrops fetalis, intrauterine fetal demise (IUFD), and when neonatal resuscitation is required. There are potentially three routes for the placenta to become infected: via maternal sepsis – the hematogenous route, via contamination of the amniotic fluid by cervicovaginal organisms – the ascending route, and via direct extension from uterine or pelvic infections. The hematogenous and ascending mechanisms each have their own characteristic pathology. In this chapter, we will review the morphologic patterns of placental infections and describe specific infections when they have characteristic pathologic features. For a more complete discussion of specific placental infections, we recommend these texts[1,2].

HEMATOGENOUSLY SPREAD INFECTIONS

Villitis: Acute and Chronic, Mixed

Definition: Inflammation of the chorionic villi due to infections. See also "Villitis of Unknown Etiology" in Chapter 13 for a discussion on noninfectious villitis.

Clinical Context: Maternal sepsis, viremia, parasitemia resulting in direct hematogenous spread to the placenta. Not all maternal infections are symptomatic, which is especially true for herpes simplex virus (HSV), syphilis, and toxoplasmosis. Infectious villitis can be associated with preterm delivery, IUGR, hydrops fetalis, and/or IUFD.

Proposed Pathogenesis: Organisms in the maternal blood reach the placenta by normal uterine circulation. Villous infection is via access of the villous stroma either by a break in the syncytiotrophoblastic layer or direct infection of the syncytiotrophoblast and resultant invasion/infection of the villous stroma and fetal vasculature. Although the precise mechanism of vertical transmission of viral infection is, for the most part, unknown[3,4,5], evidence indicates that specific receptors are present on the trophoblastic membrane for some viruses, e.g. hepatitis C virus (HCV)[6,7] and HIV[8]. In cell culture models, direct trophoblastic infection has been shown for other pathogens, viral and protozoan, e.g. hepatitis B virus (HBV)[9,10], toxoplasmosis[11], and Cytomegalovirus (CMV)[12]. Infection of the villi results in inflammation (villitis), with the inflammatory cells likely arising from both the maternal and fetal compartments.

Gross Features: Villitis is for the most part a histological diagnosis without gross findings. Some villitites have gross abnormalities when they are accompanied by macro-abscesses (see acute villitis below). These are scattered, variably sized soft gray/white parenchymal lesions (Figure 12.1) often accompanied by acute chorioamnionitis, which will present with yellow/green cloudy membranes (Figure 12.2) (see acute chorioamnionitis section below). Occasionally with high-grade chronic villitis and vascular obliteration (see section on chronic villitis below, and Chapter 13) one may find firm and pale regions of the placenta similar to those sometimes seen grossly in segmental fetal vascular malperfusion, high grade (see Chapter 10).

Microscopic Features: Villitis is inflammation of the villous stroma. The inflammatory cell type defines the villitis as either acute (neutrophils) or chronic (lymphocytes and macrophages); rarely are mixed cases encountered. Infectious villitis, as contrasted with villitis of unknown etiology (see Chapter 13), is due to hematogenously spread infections from the maternal blood stream, and these can include bacterial, viral, parasite, mycobacterial, and fungal infections. This section will discuss the infectious villitides by their histologic phenotype – the inflammatory cell type defining the villitis (either acute or chronic villitis).

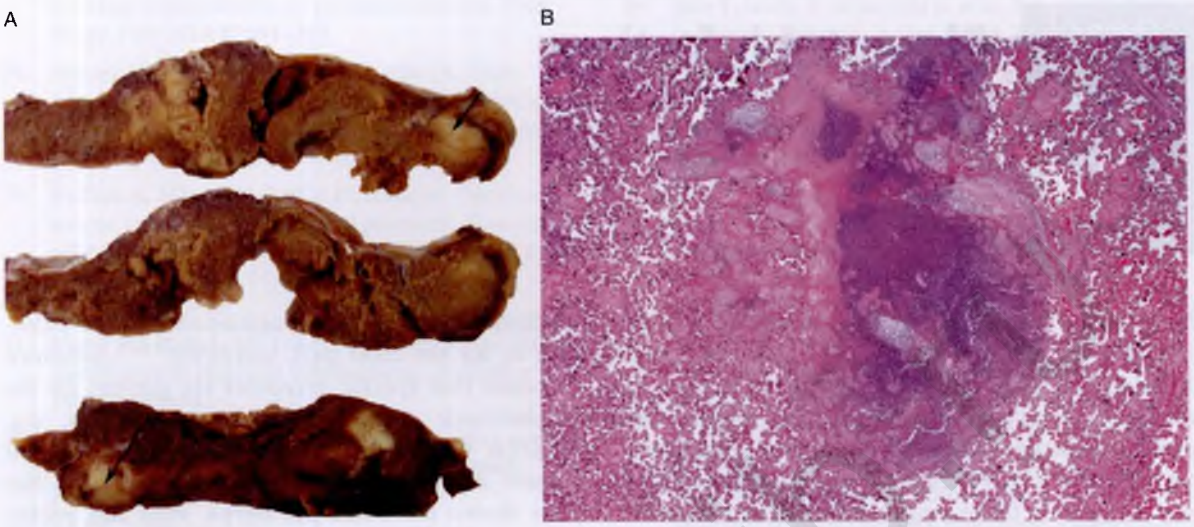

Figure 12.1 Listerial abscesses in the placenta can present with (a) grossly identifiable mass like lesions or (b) microscopic findings as seen in this image. Images courtesy of R. Redline.

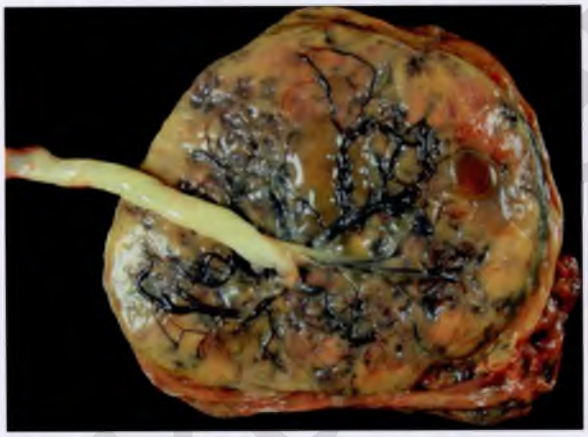

Figure 12.2 Acute chorioamnionitis with yellow cloudy discoloration of the membranes and umbilical cord.

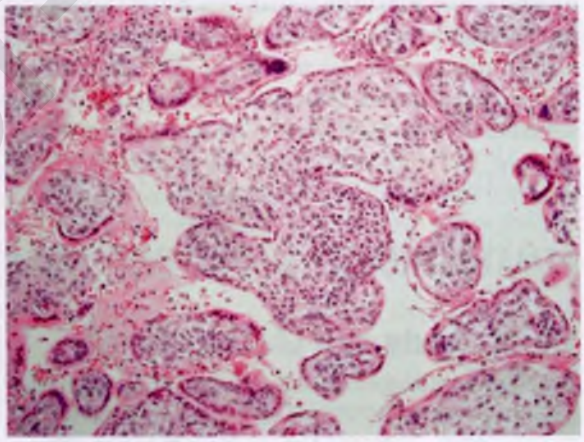

Figure 12.3 Acute villitis.

ACUTE VILLITIS

Definition: Neutrophilic villitis, generally diffusely involving the placenta with patchy, "geographically" patterned lesions (Figure 12.3).

Clinical Context: The maternal infection is usually evident with a septic picture. Often, acute villitis occurs in the setting of acute chorioamnionitis (see section below). Common organisms associated with acute villitis include *Streptococcus agalactiae* (group B streptococcus, or GBS)[13] and *Listeria monocytogenes*[14], but others have been reported more rarely and should be considered if the former are excluded. These include *Mycobacterium tuberculosis* (MTB)[15], *T. pallidum* (syphilis)[16,17], *K. pneumonia*[18], *H. influenza*[19], *C. trachomatis*[20], Coxsackievirus B3[21], and Bacillus species[22]. Perinatal complications include preterm delivery, congenital infection, and IUFD[23].

Proposed Pathogenesis: Direct infection of the villi via maternal blood (see pathogenesis section above).

Gross Features: Acute villitis has no gross findings unless it is also associated with acute chorioamnionitis and/or parenchymal abscesses (Figures 12.1 and 12.2).

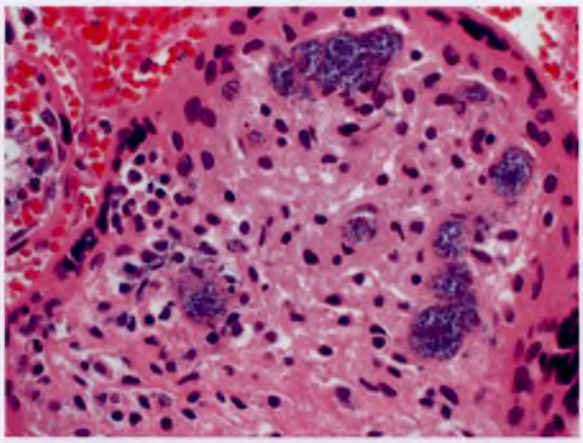

Figure 12.4 Intravascular organisms in this case of a septic abortion due to GBS.

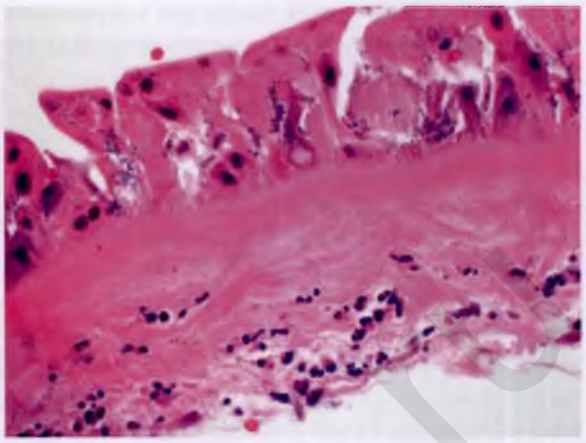

Figure 12.5 Acute chorioamnionitis maternal stage 2 grade 2 with amniotic epithelial metaplasia. Note the bacterial cocci in pairs enmeshed in the amniotic epithelium. The culture from this placenta was positive for GBS.

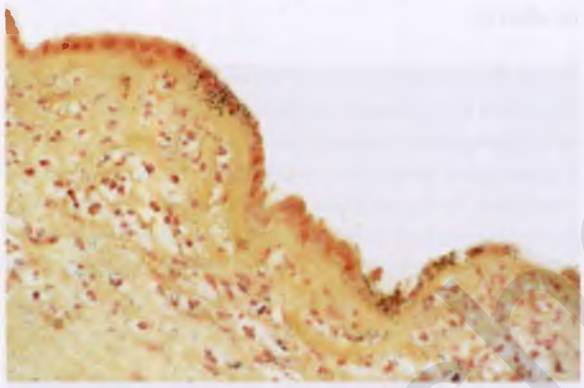

Figure 12.6 Steiner stain showing Listeria organismal overgrowth in the amniotic epithelium.

The presence of grossly identifiable abscesses is highly suggestive of placental listerial infection[24], although it has also been described in cases of MTB[15,25].

Microscopic Features: Neutrophilic infiltrate within the villous stroma, often associated with acute chorioamnionitis (see section on acute chorioamnionitis below) and intervillositis. The inflammation can be destructive. Occasionally intervillous abscesses are present, which can be large enough to see grossly (Figure 12.1). These micro- or macroscopic abscesses are characteristic of *L. monocytogenes* placentitis. Single isolated villi with acute villitis are usually due to bacterial infections, especially GBS and *E. coli*[13], which can be associated with intravascular organisms[26] (Figure 12.4). Mixed inflammatory infiltrates can be seen in syphilis[27].

Specific pathogens and pathologic features: *Group B Streptococci* (Streptococcus agalactiae): Typically GBS presents with high-stage and -grade acute chorioamnionitis, but it can be clinically and histologically "silent"[28]. It can sometimes present with acute villitis that can be marked[13]. One can occasionally identify the organism by H&E stain alone on the surface of the membranes (Figure 12.5) or intravascularly (Figure 12.4).

Listeria monocytogenes: Macro and/or microabscesses are the characteristic findings in placental listeriosis (Figures 12.1 and 12.3). Usually there is also a necrotizing acute chorioamnionitis in which the organisms will be abundant when stained with a silver stain, or tissue gram stain (will stain gram variable) (Figure 12.6). Immunohistochemical stains are available as well. Organisms can be identified in the center of the parenchymal abscesses. Other features of listerial placentitis include a "fruity" odor of the fresh placenta.

Microscopic features and suggested pathogens

Acute villitis involving single villi (spotty distribution in parenchyma, Figure 12.3): GBS and *E. coli*[13].

Acute villitis with abscesses: *L. monocytogenes*[24], MTB[15,25].

Ancillary Diagnostic Testing: When listerial infection is suspected grossly, it is important that the microbiology laboratory be alerted so that appropriate testing can be performed. *L. monocytogenes*

requires specialized growth media and temperatures for culture[29]. Special stains are recommended for confirmation in cases in which there have not been microbiologic studies. We recommend that a tissue gram stain and a silver stain (e.g. Steiner) be performed on all histologically confirmed acute villitities. Consideration for a spirochete stain (e.g. Dieterle) or acid fast bacillus stain based on clinical history and additional suggestive findings (e.g. granulomatous deciduitis in cases of MTB; heavy placenta with funisitis in syphilis, see below). For complete and specific identification of the infectious organism when cultures and special stains are not informative, one can send formalin fixed paraffin embedded tissue (FFPE) to the Infectious Disease Pathology Branch of the Centers for Disease Control and Prevention (CDC) for analysis (www.cdc.gov/ncezid/dhcpp/idpb/index.html). They have a large cadre of immunohistochemical stains, the facility for molecular speciation, and other techniques with the experience to provide excellent service.

Prognostic implications: Acute villitis is an ominous finding as the congenital infection rate is high. It is associated with overwhelming fetal sepsis and is often fatal[13] *Listeria monocytogenes* can be a lethal infection in both the mother and the fetus[30], and GBS is often lethal for the fetus/neonate[31]. Aggressive therapy is needed for live births. The diagnosis should be relayed as a critical value to the pediatrician taking care of the neonate as well as the obstetrician for the mother.

Knowledge Gaps: The origin of the inflammatory cells is currently not definitively known for acute villitis – maternal or fetal. This is of more than academic interest. In villitis of unknown etiology, an apparently noninfectious chronic inflammation of the chorionic villi (see Chapter 13), the inflammatory cells are maternal[32]. Infectious villitities may have a substantial fetal inflammatory contribution, which may be both less effective and more toxic to the fetus than a purely maternal inflammatory infiltrate, adding to their high morbidity and mortality rate[33,34].

Chronic Villitis

Definition: Chronic inflammatory infiltrate in the villous stroma, which may include lymphocytes, histiocytes, plasma cells, and/or histiocytic giant cells. Accompanying the villitis may be an associated intervillositis (chronic inflammatory cells in the intervillous space).

Clinical Context: Most chronic villitides are noninfectious and are termed "villitis of unknown etiology" (VUE). These are discussed elsewhere (see Chapter 13). A very small percentage of histologically confirmed chronic villitides are infectious, likely 1 percent or so. They tend to occur in the late second and early third trimesters, as opposed to VUE, which is typically a late third trimester/term phenomenon. Usually infectious chronic villitis is associated with significant perinatal morbidity or mortality, including IUGR, hydrops fetalis, preterm delivery, IUFD, and congenital infection.

Proposed Pathogenesis: Infection of the villi either by a breach in the syncytiotrophoblastic boundary or by direct infection of the trophoblast and subsequent infection of the stroma, vasculature, and potentially fetal blood (see proposed pathogenesis for acute villitis above).

Gross Features: Chronic villitis is usually a microscopic diagnosis. Occasionally clusters of chronic villitis can be identified grossly as small pale and firm regions in the parenchyma. Most cases of infectious chronic villitis are associated with small placentas weighing less than the tenth percentile or large placentas weighing greater than the ninetieth percentile[35]. Some specific infections are associated with gross pathologies, including CMV with thick placentas[36] and syphilis with very large, nonhydropic, placentas[37].

Microscopic Features: In contrast to VUE, infectious chronic villitides tend to diffusely, but unevenly involve the placenta (every slide and every region within a slide, but usually not all villi, are affected). The affected villi often cluster together in patches (Figure 12.7) with the patches spread diffusely. The affected villi are hypercellular, often with sclerosis of the villous vessels (obliterative features). This can lead to "downstream" avascular (not always hypercellular) villi (Figure 12.8). The infiltrate is usually mononuclear (lymphocytes and macrophages) but can include plasma cells or histiocytic giant cells (Figure 12.9). The presence of these latter specialized cells are quite suggestive of an infectious villitis and are less common in VUE. Often, chronic villitis is associated with intervillositis, usually histiocytic (Figure 12.10). There may be an increase in perivillous fibrin as well. Trophoblastic necrosis is often present in affected villi. A common and helpful finding in infectious chronic villitis, rarer in VUE, is the

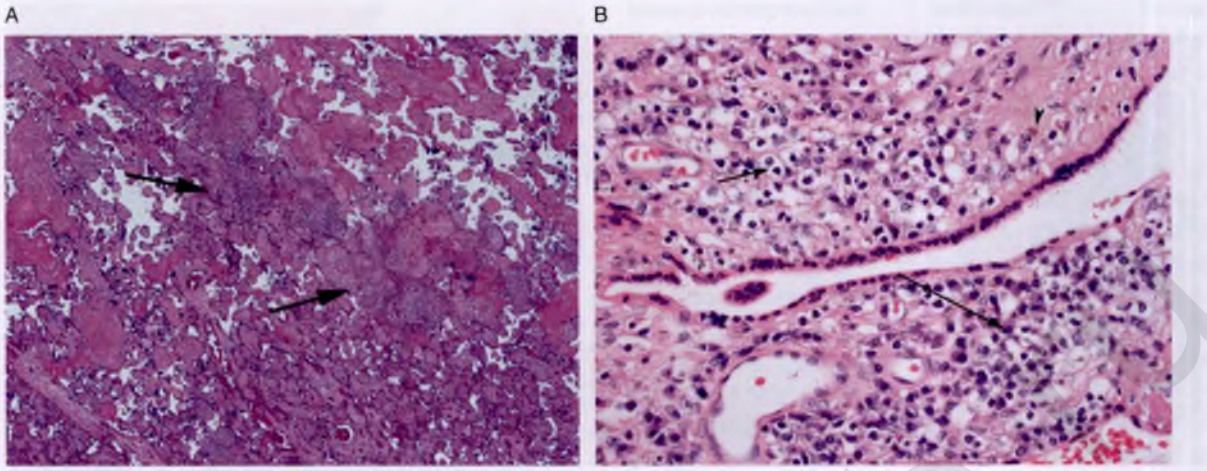

Figure 12.7 Diffuse chronic villitis. (a) low-power image from a case suspicious for infection due to the diffuseness of the chronic villitis. (b) High-power of chronic villitis from a case of CMV placentitis showing plasma cell villitis (long arrow)with hemosiderin (arrowhead). Most of the cells are lymphohistiocytic (short arrow).

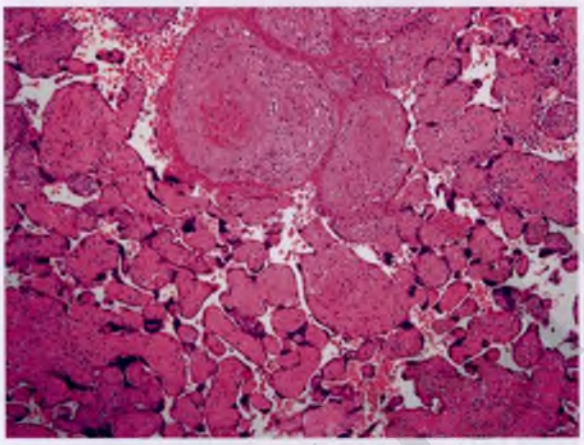

Figure 12.8 Obliterative villitis. Note avascular villi to the left and bottom of the image with the chronic villitis on top showing vascular occlusion, in this case of CMV placentitis in a live birth.

presence of immature (nucleated) red blood cells in the fetal circulation. Plasma cell deciduitis or granulomatous deciduitis, also hint to an infectious nature of the villitis.

Most infectious chronic villitities have no specific histopathological features; it is rare to find diagnostic organisms in the affected placentas, and ancillary studies (see below) are often necessary to make a specific diagnosis. Occasionally, the organism can be identified by routine hematoxylin and eosin (H&E) histology (for example viral inclusions in CMV or HSV placentitis or *T. gondii* tissue cysts), or by immunohistochemistry, or in situ hybridization. Some specific infections can be suspected based on some characteristic gross and histopathologic features; see the following.

Specific pathogens and pathologic features: *CMV:* CMV placentitis usually follows primary infections. Reactivated infections in immunocompromised individuals may also cause significant pathology[37]. Characteristic features for CMV placentitis include small, thick (>4 cm) placentas with diffuse lymphoplasmacytic villitis and villous stromal expansion with hemosiderin deposition (Figure 12.11). A common feature is the subtrophoblastic location of the villitis with associated trophoblastic necrosis (Figure 12.12). CMV placentitis is frequently accompanied with chorionic plate vascular thrombi. Plasma cells or giant cells are often present as a component of the villitis (Figure 12.9B). CMV placentitis can be subtle, and the presence of placental findings varies with gestational age at infection and the duration of the infection[38]. Only approximately 10 percent of congenital CMV have the characteristic owl's-eye nuclear inclusions[39], which are typically present in the villous stroma, endothelial cells, and occasionally in the amniocytes[38]. Some have associated increased perivillous fibrin(oid) in plaques[38,40,41]. Some documented congenital CMV cases show no placental pathology[41]. Immunohistochemistry can be useful to demonstrate viral proteins in villous stroma, villous vessels, villous endothelial cells, and amniocytes[38,40,41] and rarely in trophoblast[41].

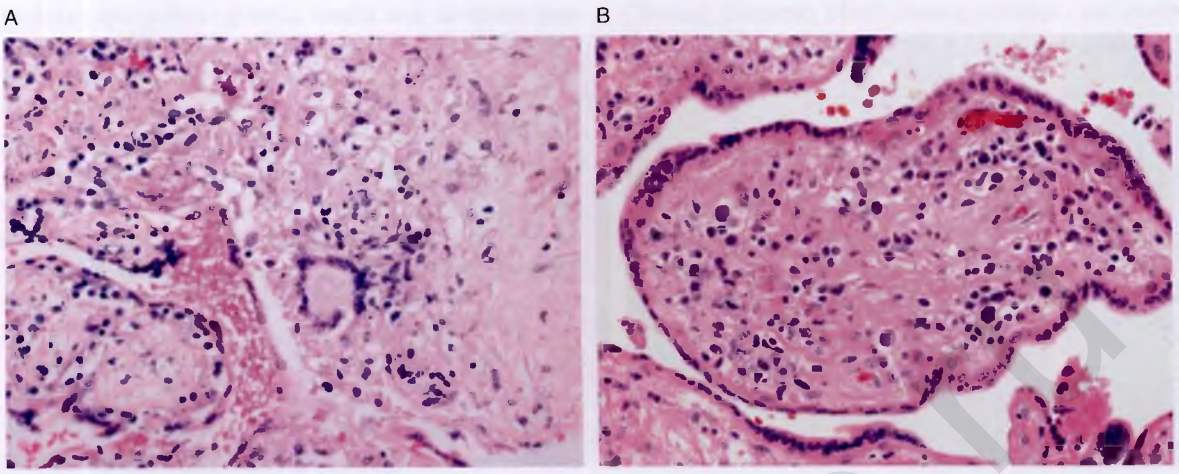

Figure 12.9 (a) Giant cell villitis in a case of toxoplasmosis and (b) plasma cell villitis in a case of CMV placentitis. Images provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

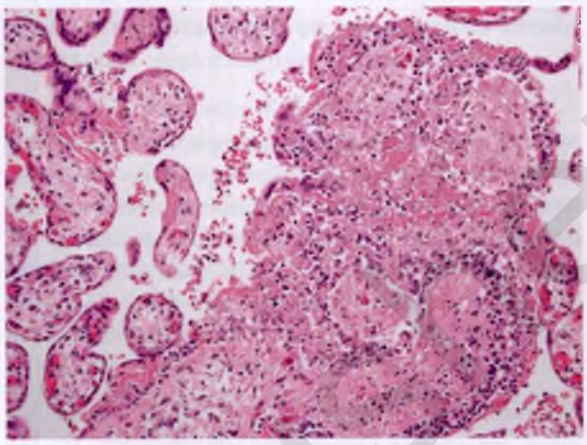

Figure 12.10 Chronic villitis with intervillositis. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

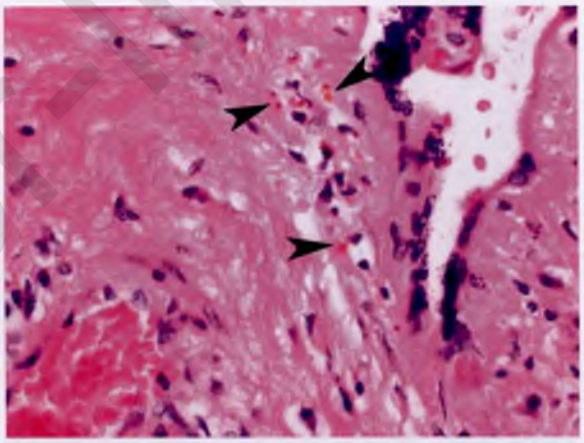

Figure 12.11 CMV placentitis with hemosiderin in villi (arrowheads).

HSV: HSV can be hematogenously spread to the placenta or may cause placentitis from the ascending route (see below). Generally serious congenital infections follow only the initial viremia from a primary infection and often are not associated with maternal signs or symptoms (without vesicles for example). When hematogenously spread, the placentas are either abnormally small or large with a striking plasma cell villitis and necrotizing deciduitis. Rare viral inclusions can be present in villous stroma. We have seen inclusions only rarely, once markedly present (although necrotic) in the umbilical cord (Figure 12.13). In ascending infections (see section below), or sometimes even with hematogenous infections, there is an acute inflammatory component with acute chorioamnionitis andnecrotizing funisitis showing plasma cells in the chorioamnionitis and in the umbilical cord Wharton's jelly (Figure 12.13a)[2]. "Blisters" have been described on the placenta due to necrotizing chorioamnionitis[2]. Specific HSV serotypes cannot be discerned by immunohistochemistry, but the proteins common to both can be identified even in necrotic tissues and can identify "ghosts" of infected cells in placental tissues (Figure 12.13b, c).

T. gondii: Placental toxoplasmosis occurs usually in primary infections, but reactivation of latent toxoplasmosis has been described in an

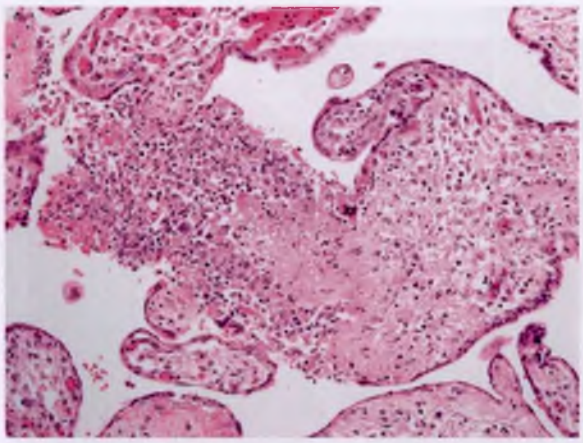

Figure 12.12 CMV placentitis in a stillbirth showing subtrophoblastic villitis and intervillositis with necrosis. Viral inclusions were present in other sections.

immunocompromised individual[42]. Rarely Toxoplasma cysts and occasionally trophozoites can be found in the umbilical cord Wharton's jelly, amniotic epithelium, and villi (Figure 12.14). Diffuse lymphoplasmacytic or granulomatous villitis is characteristic[43]. Often placental toxoplasmosis is accompanied by hydrops fetalis and placentalis[44]. There is a specific antibody useful in immunohistochemical analysis to identify cysts and trophozoites[45], often scarce in the placenta even in well documented congenital infections.

T. pallidum: Syphilitic placentas are large (heavy), pale, and nonhydropic[46] with necrotizing funisitis (see acute chorioamnionitis section below). The histopathologic features include hypercellular, inappropriately immature villi[46] with a mild mixed acute and chronic lymphoplasmacytic villitis, patchy, with endovascular proliferation and obliteration of the

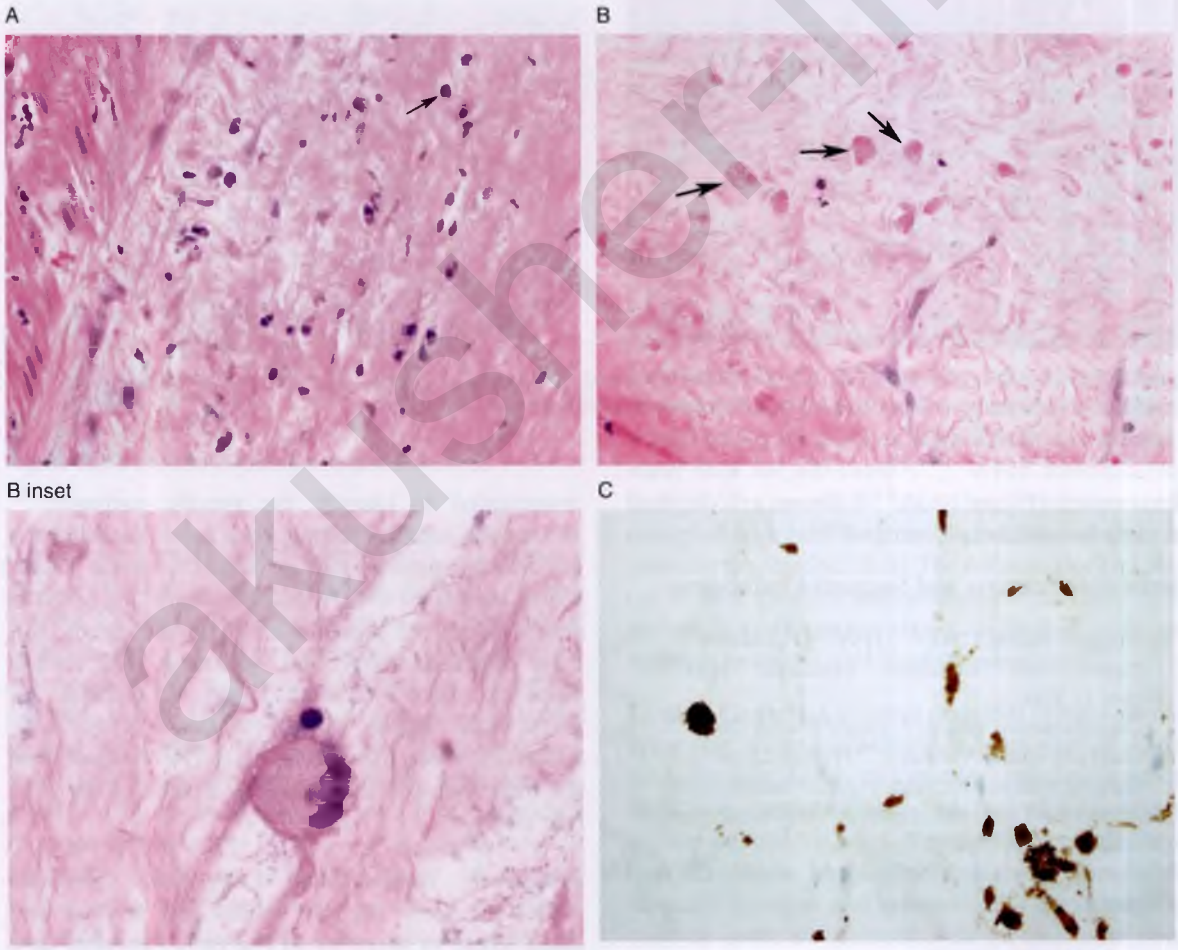

Figure 12.13 HSV involving the umbilical cord. (a) Plasma cells in Wharton's jelly (arrow). (b) Ghosts of infected stromal cells (arrows). (c) Immunoreactivity in the ghost-infected cells (HSV immunostain).

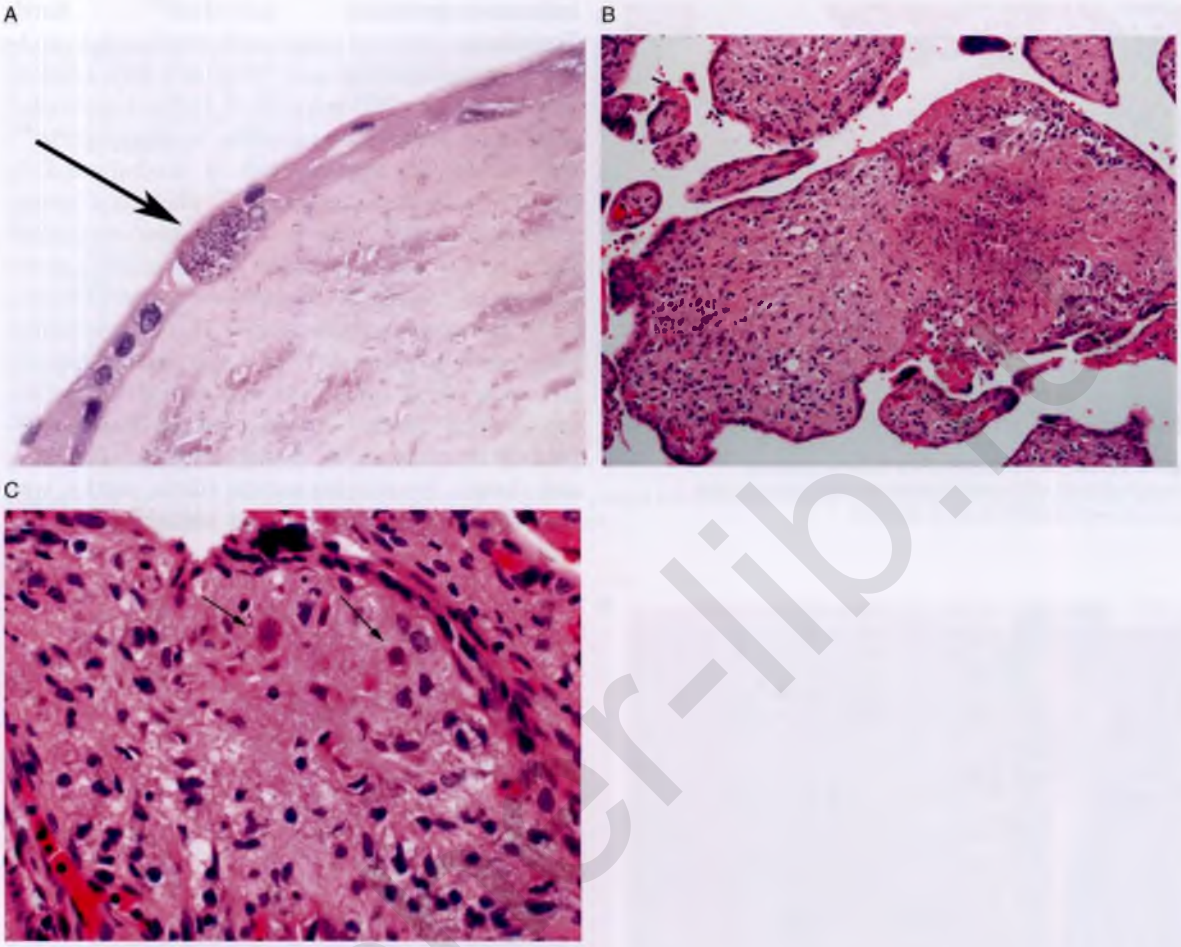

Figure 12.14 Toxoplasmosis. (a) Toxoplasma cyst in amniocyte (arrow). (b) Granulomatous villitis. (c) Encysted forms in villitis. Image (b) provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

villous vessels (Figure 12.15)[27]. Plasma cell decidual vasculitis has also been described[46].

Microscopic Features and Suggested Pathogens:

Plasmacytic villitis: CMV[47], HSV[2], *T.pallidum*[46]
Plasma cell umbilical vasculitis: HSV[2] (Figure 12.13a)
Granulomatous villitis: *T. gondii*[43] and CMV[38]
Giant cell villitis: Varicella[48] (Figure 12.16)
Chronic villitis with fetal vascular malperfusion (fetal vascular thrombi especially chorionic plate thrombi): CMV[49], HSV[50]
Chronic villitis with hemosiderin in villi: CMV (Figure 12.11)

Ancillary Diagnostic Testing: Chronic villitis with features suggestive of infection should be further investigated to identify the specific pathogen[51]. We suggest ancillary testing when any of the following features are present: diffuse villitis, preterm villitis, villitis associated with hydrops, stillbirth, or neonatal resuscitation, the presence of any of the specific features described above, and, of course, with clinical suspicion. Immunohistochemistry is available for CMV, HSV, listeria, and toxoplasmosis. Other antibodies and molecular speciation can be obtained from the Infectious Disease Pathology Branch of the CDC (see above).

Prognostic Implications: Congenital infections associated with chronic villitis are serious and often lethal in utero or in the early neonatal time period. Survivors can have significant morbidity including congenital malformations (in congenital

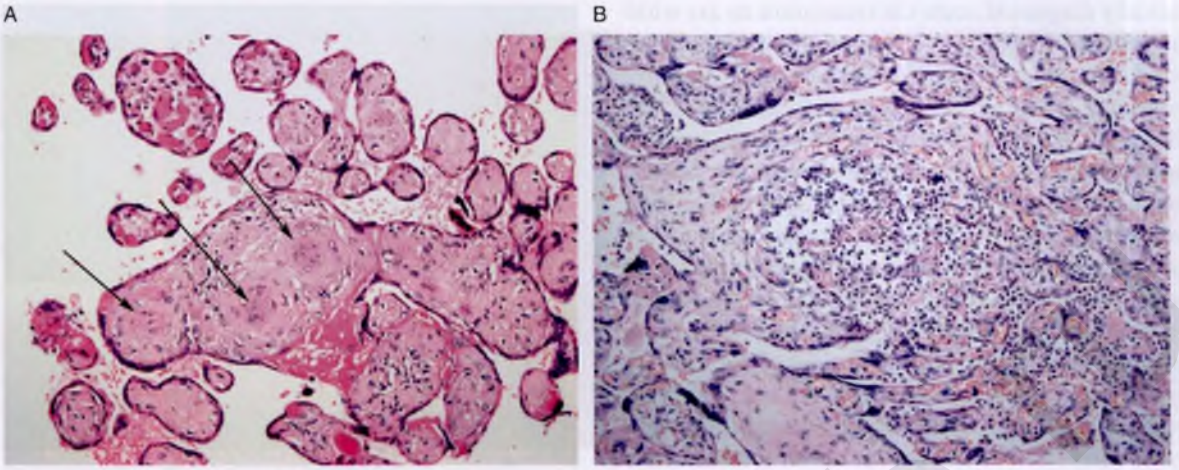

Figure 12.15 Congenital syphilis showing (a) obliterated vessels (arrows) and avascular villi and (b) acute and chronic villitis in congenital syphilis.

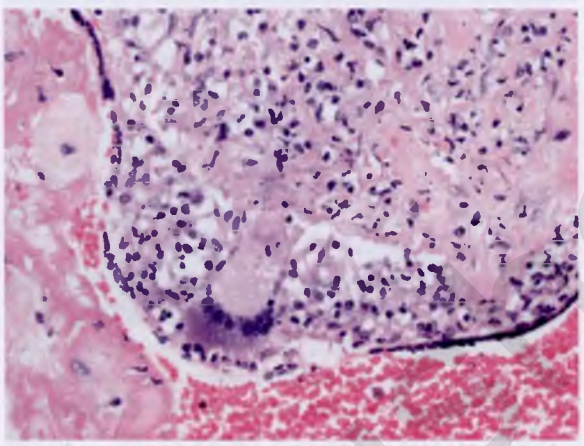

Figure 12.16 Varicella placentitis with giant cell villitis.

rubella syndrome[52] and Zika virus[53,54]), sensorineural deafness (in congenital CMV[55]), and various forms of neurocompromise[56,57] including cerebral palsy[58]. New infectious contributions are occasionally identified in cases of idiopathic chronic villitis (VUE, see Chapter 13). Recently human papilloma virus (HPV) has been identified in a percentage of cases previously diagnosed as VUE[59]. Influenza A also has also been identified in cases diagnosed as VUE[60]. It is prudent to be concerned about an infectious cause of chronic villitis whenever it is diffuse; occurs in a preterm gestation; or is associated with stillbirth, hydrops fetalis, or IUGR, with a maternal history of exposure, or with a sick neonate.

Knowledge Gaps: Much is still uncertain about the mechanism of infection in chronic villitis, whether the infection is "assisted" through the trophoblastic barrier of the placenta, or occurs via breaks/injury in the trophoblastic layer allowing direct infection of the villous stroma.

ASCENDING INFECTIONS

Acute Chorioamnionitis

Definition: Acute inflammatory cells in the amnion/chorion or subchorionic space. Acute chorioamnionitis is associated with amniotic fluid infection syndrome in many (but not all) cases[61–63]. When infectious, it is thought to occur via the "ascending" route from cervicovaginal flora breaching the placental membranes and infecting the amniotic fluid. The inflammatory response can be both maternal (inflammation in the membranes) and fetal (inflammatory cells associated with fetal vessels – umbilical cord or chorionic plate)[64].

Clinical Context: Common maternal presentations of acute chorioamnionitis include fever, uterine tenderness, preterm labor, tachycardia, purulent amniotic fluid; fetal presentations include tachycardia and nonreassuring fetal testing. Complications include abruption.[65] Acute chorioamnionitis can be defined clinically by signs and symptoms, or histopathologically by acute inflammation in the placental membranes. The correlation between the two is not perfect and in our experience about 25 percent of

clinically diagnosed acute chorioamnionitis are without histopathological confirmation. Others have found even higher rates of histologically negative chorioamnionitis in clinical chorioamnionitis[62,66]. Clinically "silent" chorioamnionitis also occurs: histological acute chorioamnionitis without clinical symptoms or signs[57,58]. The risk factors for both clinically and histopathologically diagnosed acute chorioamnionitis include prolonged rupture of membranes, prolonged labor, multiple cervicovaginal examinations, bacterial vaginosis, meconium, epidural anesthesia, tobacco and/or alcohol use, existing genital tract infection, "foreign" bodies (cerclage, pressure catheter, IUD, scalp electrodes), and prematurity[65,67,68]. The prevalence of intraamniotic infection has been reported in approximately 1–4 percent of all births overall[69], but some reports have indicated a much higher rate (up to approximately 13 percent at term[70]). The highest rate is among preterm deliveries (approximately 40–70 percent[61,67,71]). The prevalence of histological acute chorioamnionitis is unknown (as placentas are not universally examined) but is likely in the range of 5 percent or less in uncomplicated term deliveries[72].

Proposed Pathogenesis: Cervicovaginal flora reach the amniotic fluid via a breach in the placental membranes over the cervical os. This breech can be directly due to infection of the membranes and resultant inflammatory necrosis or from rupture membranes due to another noninfectious cause. The amniotic fluid provides a good growth medium for the organism that can stimulate maternal and fetal inflammatory response. Clinical sequela may be related directly to infection[73,74] or be secondary to the immune response (e.g. cytokine release), which appears to play an important role in fetal morbidity and mortality[34,61,75–77].

Gross Features: Inflammation of the membranes results in a cloudy/opaque yellow discoloration of the chorionic plate and free membranes (Figure 12.2). The fetal inflammatory response, if robust (especially with necrotizing funisitis; see below) can result in a yellow-tinged umbilical cord with halos around the vessels that are inflammatory cells (Figure 12.17). In specific situations (candidal funisitis), abscesses on the cord surface can be present and identified grossly (Figure 12.18).

Microscopic Features: The hallmark of maternal acute chorioamnionitis is neutrophil infiltration;

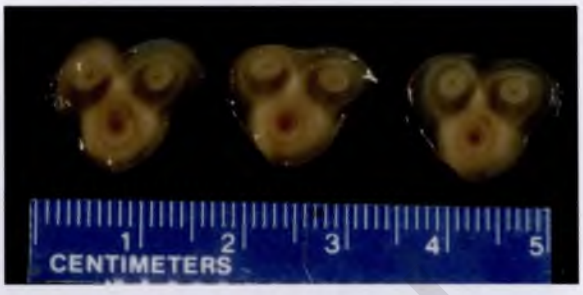

Figure 12.17 Necrotizing funisitis, umbilical cord sections showing halos around vessels.

progressing from the subchorionic space on the chorionic plate and from the chorion laeve in the free membranes, to the mesenchymal tissue between the chorionic and amniotic epithelium, and eventually the amniotic epithelium. The inflammation can be mixed with mononuclear cells, but the predominant inflammatory cell should be the neutrophil. Chronic chorioamnionitis is typically a noninfectious entity (and is discussed elsewhere; see Chapter 14) unless plasma cells are present, when one should be concerned particularly about HSV placentitis[2].The maternal inflammatory infiltrate should be staged and graded using the 2003 Redline et al. nosology (Table 12.1, Figure 12.19)[64].

The fetal inflammatory response involves fetal inflammatory cells transgressing through the fetal vessels and in high-grade cases involving the adjacent soft tissues. The fetal inflammatory response should also be staged and graded using the 2003 Redline et al. nosology criteria (Table 12.1, Figure 12.20)[64]. In this nosology, the more umbilical vessels involved, the higher the stage; and as the extent of extravascular involvement increases, so does the grade. Although usually the fetal inflammatory response accompanies a maternal inflammatory response, it can be present as an isolated finding[71].

There are two categories of acute chorioamnionitis that deserve more description: necrotizing acute chorioamnionitis (not to be confused with subacute chorioamnionitis, see below), which is a maternal response; and necrotizing funisitis (also called subacute funisitis and concentric umbilical perivasculitis), a fetal inflammatory response. These involve characteristic patterns of inflammation in which neutrophil debris, and sometime calcification, is a prominent feature (Figures 12.17 and 12.20c).

The morphology of infectious acute chorioamnionitis is usually nonspecific, and many different

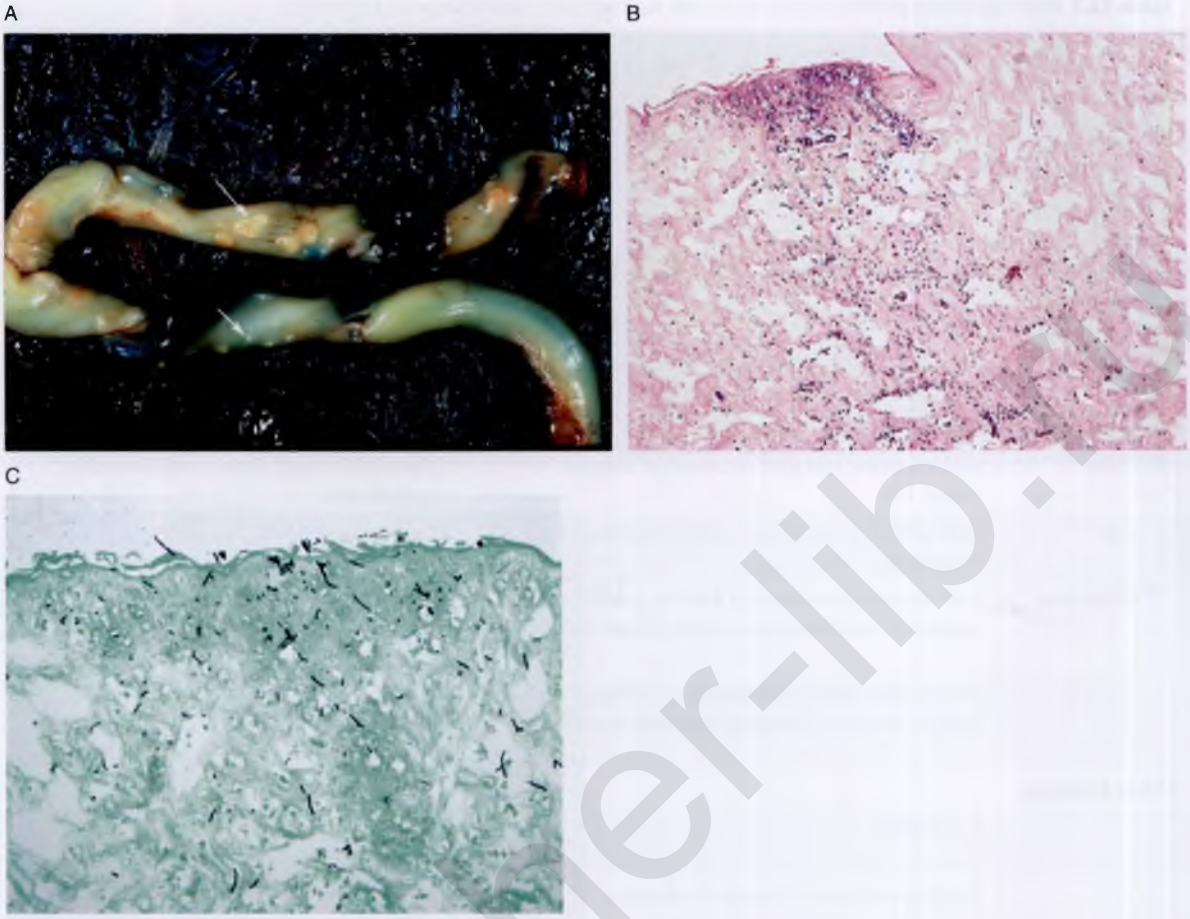

Figure 12.18 *Candida albicans* placentitis. (a) Gross image of a placenta with multiple candidal abscesses on the umbilical cord (highlighted by white arrows). (b) Photomicrograph of an umbilical cord with surface abscess. (c) GMS stain highlighting invasive fungi. Images provided with courtesy of R. Redline.

organisms can be associated with the same histopathology. Bacterial organisms are the primary cause of infectious chorioamnionitis. GBS, *E. coli*, enterococcus, *L. monocytogenes*, mycoplasma, ureaplasma, and others have all been reported in acute chorioamnionitis[78]. Fungal organisms also can be virulent, causing acute chorioamnionitis with *candida albicans* and *candida glabrata* predominating[79–81]. Other fungal organisms have been reported in acute chorioamnionitis or chronic villitis but are rare[1].

Although most infectious chorioamnionitis has nonspecific features, there are some morphologic patterns that suggest specific pathogens; these include:

Necrotizing acute chorioamnionitis: This pathology is characterized by a confluent band of neutrophils and nuclear debris along the amniotic surface (Figure 12.19c). This is a stage 3, grade 2 maternal inflammation and suggests fusobacterium, GBS, or *E. coli*.

Necrotizing funisitis: Characterized by halos of inflammation and nuclear debris, sometimes calcified, around umbilical and chorionic plate vessels oriented towards the amniotic cavity (Figures 12.17 and 12.20c) is a fetal inflammatory response stage 3, grade 2. This pattern can be noninfectious but is characteristic of *T. pallidum*[82,83] and HSV[84] infections. The presence of plasma cells in the funisitis is a distinctive feature that has been described in HSV[2,85] (Figure 12.13a). Calcific necrotizing funisitis has also been described in cases of toxoplasmosis[86].

Umbilical cord surface abscesses: A brisk fetal inflammatory response (typically stage 2, grade 2) associated with surface umbilical cord inflammation with abscess formation is nearly pathognomonic of candida albicans placentitis[80] (Figure 12.18), but we have also seen this pattern rarely with GBS infection.

Table 12.1 Placenta reaction patterns related to amniotic fluid infection: nomenclature and definitions

	Diagnostic terminology	Definition
Maternal inflammatory response:		
Early	*Acute subchorionitis/ Acute chorionitis (Stage 1/3),*	PMN* in subchorionic fibrin and/or membrane trophoblast
(NOS)§	*Acute chorioamnionitis (Stage 2/3)*	Diffuse-patchy PMN* in fibrous chorion and/ or amnion
Prolonged	*Necrotizing chorioamnionitis (Stage 3/3)*	PMN karyorhexis, amniocyte necrosis, and/or amnion basement membrane thickening/ hypereosinophilia
Severe	*Severe acute chorioamnionitis or with subchorionic microabsesses (Grade 2/2)*	confluent PMN (≥ 10×20 cells in extent) between chorion and decidua
Fetal inflammatory response:		
Early	*with chorionic vasculitis or umbilical phlebitis (Stage 1/3)*	intramural PMN-chorionic vessels and/or umbilical vein
(NOS) §	*with umbilical arteritis or umbilical panvasculitis (Stage 2/3)*	intramural PMN- umbilical artery(ies) (± umbilical vein)
Prolonged	*with (subacute) necrotizing funisitis or with concentric umbilical perivasculitis (Stage 3/3)*	PMN ± associated debris in concentric bands-rings-halos around one or more umbilical vessels
Severe	*with a severe fetal inflammatory response or with intense chorionic (umbilical) vasculitis (Grade 2/2)*	confluent-near confluent intramural PMN-chorionic and/or umbilical vessels with attenuation/ degeneration of VSMC¶
Other features:		
	Acute villitis	PMN in villous stroma (or between trophoblast and stroma)
	Acute intervillositis/ intervillous abscesses	patchy-diffuse PMN in perivillous fibrin and/ or intervillous space
	Peripheral funisitis	focal aggregates of PMN below the umbilical surface epithelium
	Fetal vessel thrombi	recent thrombosis associated with intramural PMN
	Decidual plasma cells	unequivocal plasma cells in decidua basalis or capsularis
	Chronic (or subacute) chorioamnionitis	significant mononuclear cell infiltrate superimposed on PMN response

* PMN = polymorphonuclear leukocyte
§ NOS = not otherwise specified
¶ VSMC = vascular smooth muscle cell

Ancillary Diagnostic Testing: Culture of the chorionic plate has been recommended in cases of stillbirth or NICU admission for the possibility of congenital sepsis or in other extreme cases or clinical conundrums associated with acute chorioamnionitis. One can strip the amnion off the chorionic plate and either take a small sample of the chorionic surface (preferred) using sterile tools or swab the chorionic plate using a culture cuvette. This material can be sent for routine culture and sensitivity testing in the microbiology laboratory or for directed studies as guided by the clinical history and gross findings of the

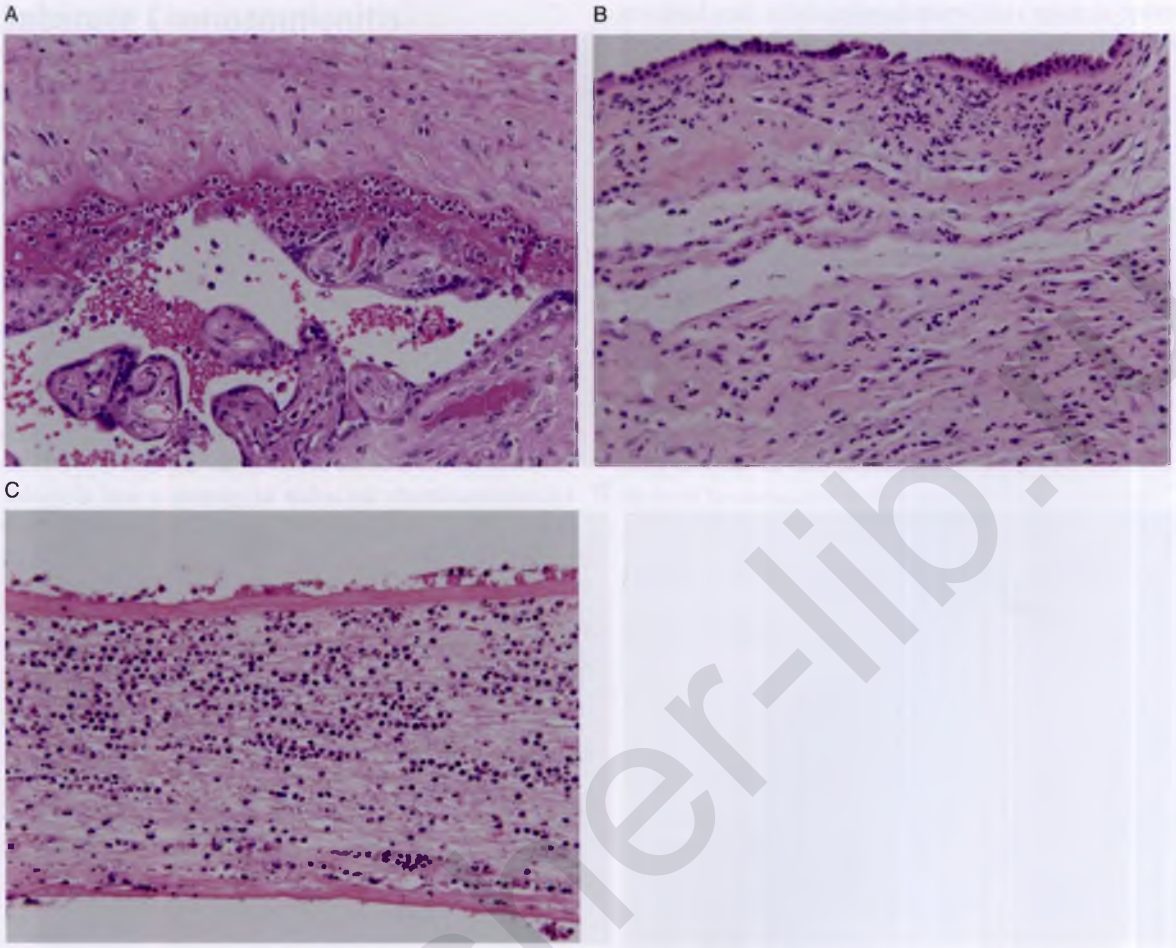

Figure 12.19 Maternal inflammatory response in acute chorioamnionitis. (a) Stage 1: subchorionitis. (b) Stage 2: chorioamnionitis, (c) Stage 3: necrotizing chorioamnionitis. Images provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

placenta. Special stains for organisms can also be performed if cultures were not taken. A tissue gram stain, fungal stain, and spirochete stain can be useful in suspected cases of specific infections. In unusual cases or those in which fresh tissue was not available for microbiologic study, formalin fixed and paraffin embedded tissue can be sent for analysis to the Infectious Disease Pathology Branch of the CDC.

Prognostic Implications: Neonatal infection associated with acute chorioamnionitis can be lethal and must be treated aggressively. Specific information provided early from the pathologic examination is helpful to the clinicians caring for the neonate. For example, the presence of umbilical cord abscesses strongly suggests *C. albicans* as the infectious organism, and alerting the clinicians to this possibility may provide impetus to treat with antifungals potentially before the culture result returns. Perinatal morbidities associated with histologically confirmed chorioamnionitis are many[87], primarily affecting the preterm neonate and include congenital/neonatal sepsis[88], increased risk for respiratory complications including pneumonia and bronchopulmonary dysplasia[89–91], increased risk for developing necrotizing enterocolitis[92], speech and hearing deficits/delay[93], and neurodisability[94,95]. An association of chorioamnionitis with patent ductus arteriosus is controversial[89,91]. Many studies have found an association of chorioamnionitis with cerebral palsy[96–98]. Outcomes for the neonate are more severe when accompanied with the presence of fetal inflammatory response[95,97,99], especially if the

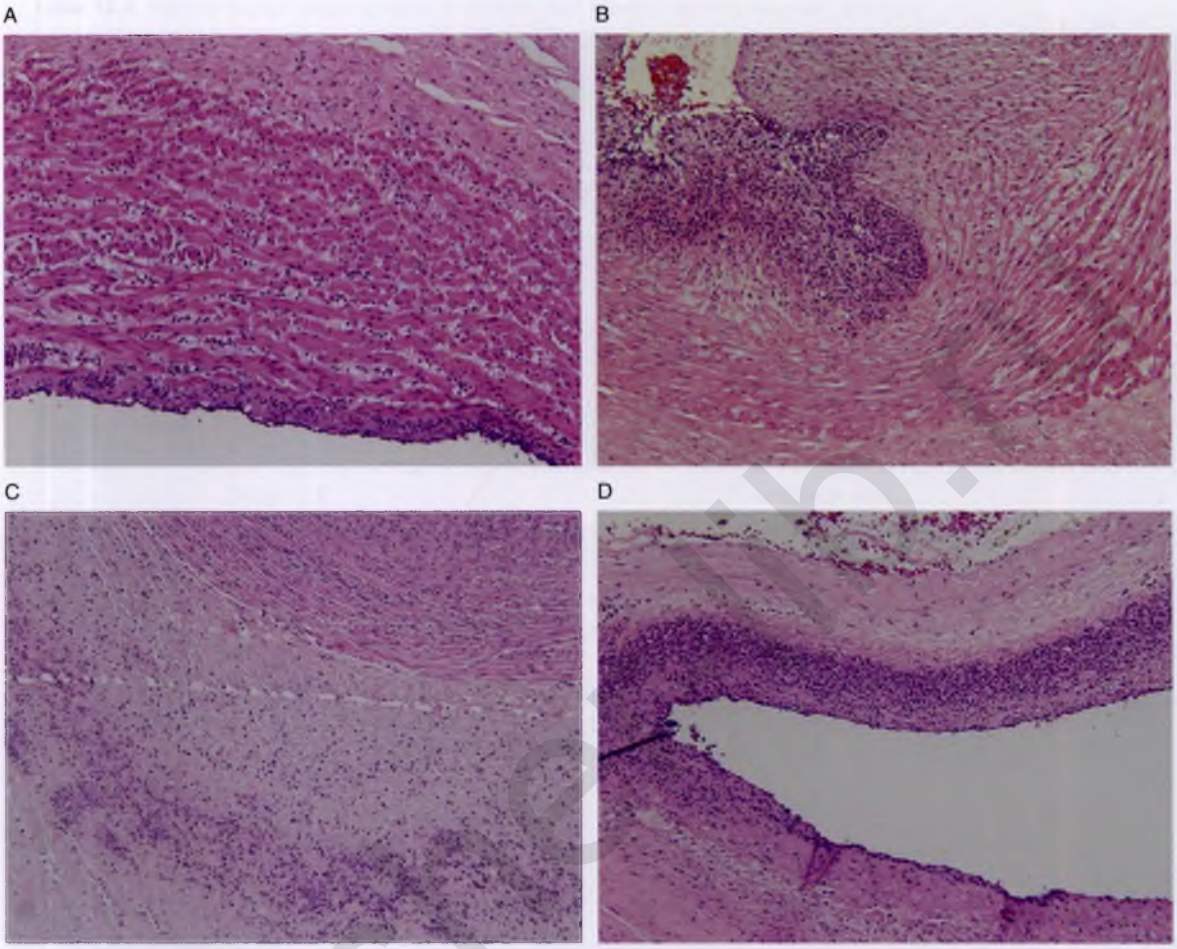

Figure 12.20 Fetal inflammatory response in acute chorioamnionitis. (a) Stage 1: umbilical phlebitis/ vein, (b) Stage 2: umbilical arteritis, (c) Stage 3: concentric umbilical perivasculitis, (d) Severe (grade 2/2) fetal inflammatory response in chorionic vessels. Images provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

umbilical arteries[87] or chorionic plate vessels[97] are involved. Robust chorionic plate vasculitis has been associated with cerebral palsy in very low birth weight infants[100] and intraventricular hemorrhage independent of gestational age[89]. Fetal/neonatal mortality is increased with histological chorioamnionitis[97]. Although the etiology of the morbidity and mortality is in large part infectious, it has been shown that inflammation alone, not the infection, is likely the key to the morbidity seen with fetal inflammatory response[101]. Obstetric complications include an association with acute and subacute abruption[102,103] (see Chapter 8) and preterm delivery, which may be influenced by race/ethnicity[104]. The maternal sequela of chorioamnionitis can also be severe. Approximately 10 percent of cases are associated with a maternal bacteremia which can lead to septic complications[105]. Other complications include dysfunctional labor, postpartum hemorrhage, and increased cesarean delivery risk[65]. We have observed a high rate of chorioamnionitis preceding uterine atony and postpartum hemorrhage requiring gravid hysterectomy.

Knowledge Gaps: In most series of acute chorioamnionitis there remain a percentage of cases in which an infectious organism is not identified[61,62,106]. These cases of "aseptic" or "sterile" acute chorioamnionitis appear to be more common in the term gestation and may be related to epidural anesthesia[63]. This data is controversial and requires further study.

Subacute Chorioamnionitis

Definition: A pattern of acute chorioamnionitis differing from the usual type in which instead of an infiltrate of well-preserved neutrophils in the subchorionic, chorion, and amniotic tissues (in usual acute chorioamnionitis), there is a degenerative mixed mononuclear and neutrophilic infiltrate more prominent in the subamniotic tissues with less prominence in the chorion and subchorion[107].

Clinical Context: Subacute chorioamnionitis presents similarly to usual-type acute chorioamnionitis with maternal fever, elevated white blood cells, premature rupture of membranes, and preterm labor and delivery. Neonatal early onset infectious symptomatology is less common in subacute chorioamnionitis than usual-type acute chorioamnionitis, and it is less likely to be microbiologically culture positive[107].

Proposed Pathogenesis: One hypothesis is that subacute chorioamnionitis represents an ascending route of infection with less potent pathogens[107]. It may represent an indolent infection[108].

Gross Features: Subacute chorioamnionitis shows gross features similar to usual-type acute chorioamnionitis with yellow, cloudy membranes. When associated with amnion necrosis (see "Microscopic Features" below), the membranes have been described as "opaque and often reddish-tan in color"[107].

Microscopic Features: The membranes and chorionic plate show a mixed acute and chronic degenerating inflammatory cell infiltrate more prominent in the subamniotic region (Figure 12.21). The chorion is minimally involved and subchorionic/intervillous space is spared. There is often associated amniotic epithelial necrosis. Chorionic edema has been described[107].

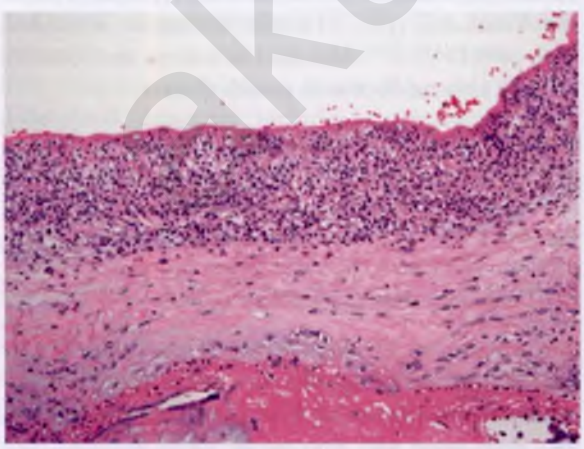

Figure 12.21 Subacute chorioamnionitis.

Ancillary Testing: Subacute chorioamnionitis has been associated with candidal infections[107]. We presume that many of these cases may be due to an indolent ureaplasma infection, as both are strongly associated with chronic lung disease[109,110,107] Diagnostic microbiologic testing for this organism should be considered if clinically warranted.

Prognostic Implications: There is a strong association of subacute chorioamnionitis, when associated with amnion necrosis, with the development of chronic lung disease in the neonates; in these cases, it is less likely to be associated with acute respiratory distress[107].

OTHER PATTERNS OF PLACENTAL INFECTIONS

Intervillositis

Definition: Intervillositis is the presence of inflammatory cells in the intervillous space (maternal lakes) usually not associated with villitis or acute chorioamnionitis. The inflammatory cells are typically mononuclear and often histiocytes, but acute inflammatory cells can be present as well. This entity may be confused with chronic histiocytic intervillositis (a.k.a. "massive chronic intervillositis"), which is a noninfectious pathology discussed in Chapter 15.

Clinical Context: This is a rare finding when associated with infection, and therefore there is usually a clinical suspicion for infection from maternal symptoms or the clinical scenario. The reported causes of infectious intervillositis are malaria[111], Zika virus (in first trimester placentas[53,112]), Dengue virus[113], and with acute inflammation in psittacosis[114].

Proposed Pathogenesis: Maternal hematogenous spread to the intervillous space with resultant sequestration and inflammatory response in the intervillous space.

Gross Features: The placenta in cases of intervillositis is typically grossly normal in appearance.

Microscopic Features: The intervillous space is filled with maternal inflammatory cells. In the case of malarial placentitis, the inflammatory cells are histiocytes

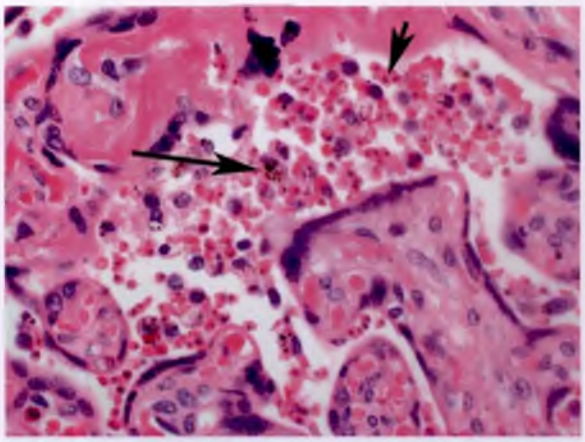

Figure 12.22 Placental involvement by malaria. *P. Falciparum* infected maternal red blood cells (short arrow) are numerous. Pigment in intervillous histiocytes present as well (long arrow). Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

and the associated maternal red blood cells (RBCs) are parasitized in great numbers (malarial sequestration, Figure 12.22). Congenital malaria is also possible therefore one must carefully screen the fetal blood for parasitized RBCs. With Chlamydia psittaci infection, the intervillositis is marked, acute, and associated with perivillous fibrin and villous necrosis. Characteristic basophilic intracytoplasmic inclusions can be identified in the villous syncytiotrophoblast[114]. A single case of first trimester placental tissue with documented ZIKV infection has been described with an intervillositis resembling chronic histiocytic intervillositis[53,112] (see Chapter 15).

Ancillary Diagnostic Testing: Confirmation of infection can be made by PCR for psittacosis[115]. Malarial sequestration is usually easily pathologically diagnosed and therefore needs no ancillary studies. One will see numerous parasitized maternal red blood cells admixed with histiocytes (Figure 12.22). Descriptions of Zika viral infection and placental pathology are rare, and confirmation is necessary and can be done by PCR and immunohistochemistry at specific state departments of public health and at the CDC's Infectious Disease Pathology branch.

Prognostic Implications: These three infections (malaria, Zika, and psittacosis) are all associated with significant fetal morbidity and mortality. The fetus can be markedly hypoxic in malarial sequestration due to the poor oxygen delivery of parasitized RBCs. Congenital malaria is also rare but reported[116]. Zika virus infection with vertical transmission has been associated with severe neuropathological complications in the fetus, with microcephaly, ocular pathology, arthrogryposis, and IUGR predominating[54,117,118]. Maternal disease is mild in Zika virus infection; it is severe in malarial sequestration and in psittacosis. Maternal disease in malarial sequestration can be associated with preeclampsia[119,120], although there might not be a direct increased risk[121]. Chlamydia psittacosis in pregnancy causes a severe febrile illness with serious complications including diffuse intravascular coagulation, liver and renal compromise, and miscarriage[114].

Marked Increase in Intervillous Fibrin/Fibrinoid (Massive Perivillous Fibrin Deposition (MPFD), Maternal Floor Infarct (MFI)

Definition: Increased perivillous/intervillous fibrin or fibrinoid material diffusely throughout the maternal space (massive perivillous fibrin deposition, MPFD) or concentrated along the maternal floor (maternal floor infarct, MFI). Focal or regional increased perivillous fibrin is occasionally present at term or at the margins at almost any gestational age and is not pathologic in a normal-sized placenta. If the fibrin/fibrinoid material is diffuse (present on every slide and in nearly every focus), then the finding is pathologic. This topic is discussed in more detail in Chapter 17.

Clinical Context: MPFD is another rare pathology of unclear etiology usually ascribed to noninfectious causes (see Chapter 17). It has been reported 3 times that Coxsackie virus A16 infection can be associated with MPFD[122–124]. Maternal infections are clinically evident as hand-foot-and-mouth disease.

Proposed Pathogenesis: Hematogenous spread of the virus with infection of the villous trophoblast resulting in trophoblastic damage, necrosis, and denudation of the villi which presents a thrombogenic nidus. Other hypothesis include excessive secretion of matrix-type fibrinoid from the extravillous trophoblast[123].

Gross Features: The placenta is pale and diffusely firm but not gritty or sponge-like. The fibrin/fibrinoid material may be interlacing or solid and will be gray-pink in the fresh state and gray-white formalin fixed (see Chapter 17).

Microscopic Features: The intervillous space is diffusely occupied by densely eosinophillic waxy and opaque material often encasing the villi and occasionally speckled with inflammatory cells. The inflammatory cells should be a minor component. The villi may show trophoblastic necrosis and denudation.

Ancillary Diagnostic Testing: Immunostaining can highlight the viral presence in syncytiotrophoblastic nuclei, and viral particles can be seen by electronmicroscopy[122]. PCR testing is available, and placental or umbilical cord samples can be tested[123].

Prognostic Implications: The reports of congenital Coxsackie virus infection include a wide spectrum of clinical outcomes including stillbirth [122–124], spontaneous abortion, neonatal complications including myocarditis, meningoencephalitis, and neurodisability. However, unaffected live births have been reported with confirmed placental infections[125,126].

Knowledge Gaps: It is unclear how what percent of MPFD may be due to Coxsackie virus infection. There appears to be no pathologic features to distinguish the more common noninfectious MPFD and the infectious MPFD. Authors have suggested that Coxsackie virus should be considered in any case of MPFD with associated chronic villitis or villous necrosis[122].

Acute Purulent Myometritis

A particularly dramatic infection of group A streptococcal infection can occur late in pregnancy that portends a dire prognosis for both the fetus and the mother[127]. An antecedent upper respiratory infection followed by sepsis and hematogenously spread bacteria results in infection as a purulent myometritis and usual secondary shock[127–129]. The histologic picture is of a necrotizing acute myometritis with little evidence of infection in the placenta[127]. The differential diagnosis includes an extracutaneous manifestation of the very rare Sweet syndrome presenting during pregnancy, as we have seen at the Massachusetts General Hospital[130].

Pathologically "Silent" Congenital Infections

Many congenital infections occur without associated gross or histopathologic features in the placenta. These include (a partial list only) the hepatitis B and C viruses, HIV, and Zika virus (other than early placental findings in spontaneous abortions). Data shows that trophoblasts can be infected with these viruses, but no morphologic changes in the placental tissues occur[131,132]. Parvovirus is another infection that is not associated with placental pathology, but one can make the diagnosis based on diagnostic inclusions in the nucleated fetal red blood cells circulating in the fetal vessels of the placenta (Figure 12.23). We have seen a case of congenital CMV with diagnostic viral inclusions in the villi but without any inflammation (presumably a very acute infection). It is humbling to keep in mind that many infections are pathologically "silent" yet can be devastating to the gestation. Sometimes all the pathologist can do is exclude specific infections in suspected cases. One should have a low threshold to order special studies to exclude congenital/placental infections in those cases associated with stillbirth, neonatal demise, severe IUGR, sick neonates, and hydrops fetalis[133].

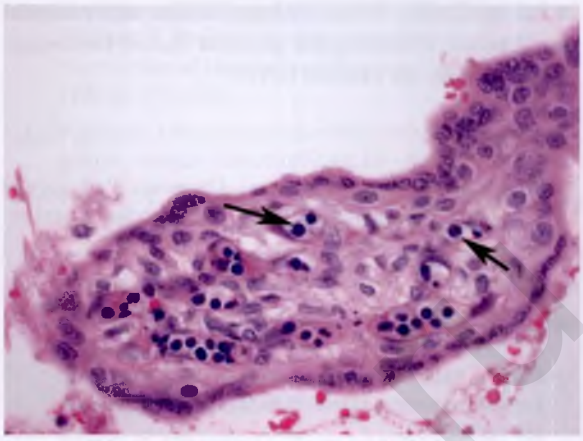

Figure 12.23 Parvovirus in circulating fetal red blood cells (arrows).

Summary and Conclusions

Placental infections are associated with significant fetal sequela whether congenital infection occurs or not, due to the pathologic processes in affected placentas[134]. A high index of suspicion for an infectious etiology is justified for any inflammatory pathology in the placenta, especially in cases of large or small placentas, thick placentas, diffuse chronic villitis, any acute villitis, placental or umbilical cord abscesses, necrotizing acute chorioamnionitis, necrotizing funisitis, plasma cell villitis, presence of hemosiderin in the villi, and of course with clinical findings such as maternal fever, exposure, documented infections and fetal/neonatal complications

including IUGR, IUFD, hydrops fetalis, and neonatal resuscitation, Culturing the placenta should be considered, especially for cases of IUFD.

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Chapter 13

Chronic Villitis / Villitis of Unknown Etiology (VUE)

Mana Parast

Villitis of Unknown Etiology (Chronic Villitis of Unknown Etiology, Villitis of Unknown Aetiology, and Idiopathic Chronic Villitis)

Definition: Villitis of unknown etiology (VUE) is defined as a primarily lymphohistiocytic infiltrate involving chorionic villi, in the absence of an *identifiable* infectious etiology.

Clinical Context: VUE was first distinguished from infectious villitis by Altshuler and Russell in 1975[1,2]. Nevertheless, it remains an underrecognized and underappreciated lesion by both pathologists and obstetricians[2]. The incidence of VUE in most studies is between 5–15 percent, with the majority occurring in term placentas. Most cases are associated with a normal term pregnancy and a normal newborn. Nevertheless, if low-grade lesions (see below) are discounted, there is an association of VUE with adverse perinatal outcomes, including intrauterine growth restriction (IUGR) and stillbirth[3,4]. Less well-established is an association with preterm birth[5]. Most recently, an increased incidence of VUE has been confirmed among obese patients, independent of coexisting diabetes and hypertensive disease. Interestingly, among the obese population, there is an almost twofold higher incidence of this lesion in placentas associated with female offspring[6]. Severe cases of VUE, particularly when avascular villi and/or stem vessel obliteration ("obliterative fetal vasculopathy") are also present (see below), have been associated with neurologic impairment, including neonatal encephalopathy and cerebral palsy, in the newborn. Recurrence rates are estimated at 10–15 percent, and are more common among high-grade cases, especially when the lesion is associated with perivillous fibrin deposition[3].

Proposed Pathogenesis: There has been much speculation about an immune basis for this lesion, based on its increased incidence among patients with autoimmune disease[5] and in IVF pregnancies with donor eggs[7]. The inflammatory infiltrate in VUE is primarily maternal in origin, comprised of both T cells and monocyte-macrophages; however, fetal macrophages (Hofbauer cells) are also present, albeit as a smaller proportion (~12 percent of intravillous macrophages). Maternal T cells are primarily $CD8^+$, and are thought to be generated against fetal antigens, though a specific inciting antigen has yet to be identified. Similarly, it is not known whether the initial antigen presentation is carried out by maternal or fetal cells. Nevertheless, fetal Hofbauer cells in VUE are hyperplastic (expressing Ki67), and are known to increase their expression of MHC class II as gestational age increases. The latter may explain why VUE is more common at term, if indeed the Hofbauer cells are involved in the initial antigen presentation. Interestingly, induction of MHC class II, as well as an increase in ICAM-I expression, have also been noted in some studies in syncytiotrophoblast at sites of VUE; however, it is not clear whether this is a cause of (versus a response to) the inflammation[5]. Similarly, phosphorylated STAT1 has been detected in some syncytiotrophoblast in the setting of VUE, indicating aberrant activation of the JAK-STAT pathway in this lesion[8]. Persistence of fetal antigen-specific (memory) T cells and an increase in their numbers after subsequent pregnancies are thought to be the mechanism of recurrence in these lesions[5]. Recently, a new T cell subtype, called regulatory T cells (Treg), which are thought to play a role in immune tolerance, have been identified at the maternal-fetal interface[9]. In pregnancies with a significant mismatch between maternal and fetal HLA-C alleles, these cells are found in even greater numbers in the decidua[10]. Most recently, placentas with VUE were found to be enriched in these Treg cells. Whether these cells play a role in genesis of the lesion, or are recruited in an attempt to dampen the anti-fetal antigen immune response remains to be determined[8].

Figure 13.1 A term placenta, bread-loafed to show extensive perivillous fibrin deposition, which was histologically found to be associated with VUE.

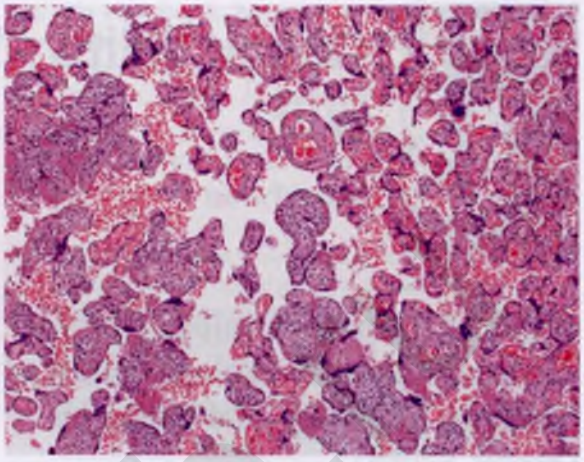

Figure 13.2 Low-power view of a case of patchy high-grade VUE (left). Uninvolved villi (right) are structurally normal.

A role for the humoral response has also been suggested in VUE. Two studies have indicated an association of VUE, including a villous lymphoplasmacytic infiltrate, with fetal/neonatal alloimmune thrombocytopenia[11][12], with one study showing alleviation of this lesion in patients treated with intravenous immunoglobulin[11]. Another study has shown increased C4d staining around syncytiotrophoblast and fetal endothelial cells in VUE, indicating a response akin to that seen in graft rejection[13].

Gross Features: Placentas with VUE may be small, particularly in cases with a high grade/diffuse lesion, or with avascular villi (see below). However, in cases with increased perivillous fibrin deposition, the placenta can be heavy (>ninetieth percentile disc weight) (Figure 13.1). Villitis by itself is often not grossly evident. The recommended submission of 3 full-thickness sections of a grossly normal-appearing placenta is estimated to diagnose ~60 percent of cases with VUE; an additional 3–4 sections are needed to diagnose 85 percent of such cases[2].

Microscopic Features: Nonuniform involvement of the placental parenchyma is a hallmark feature that distinguishes VUE from villitis of infectious etiology; the uninvolved parenchyma is often histologically normal (Figure 13.2). The villi are predominantly involved by a lymphohistiocytic infiltrate (Figure 13.3), although rarely, neutrophils and granulomas may also be present. The presence of the latter two, particularly if multifocal, should raise suspicion for an infectious etiology. Similarly, plasma cells can be part of the VUE infiltrate (Figure 13.4), particularly noted in the setting of fetal/neonatal alloimmune thrombocytopenia; however, their presence should alert the pathologist to potential infectious causes (see Chapter 12), including syphilis and CMV (Figure 13.5). We have also noted plasma cells in the setting of Zika virus infection of the placenta (Figure 13.6).

Subtypes

The pattern of distribution of VUE in the placental disc is also variable, and can be predominantly subchorionic/midparenchymal or basal/parabasal. The former is often more severe and can involve large stem villous vessels leading to luminal obliteration and large areas of avascular villi ("obliterative fetal vasculopathy", Figure 13.7). The subchorionic/midparenchymal lesions should also be carefully reviewed for an infectious etiology, particularly if they contain a neutrophilic infiltrate (Figure 13.8). Basal lesions, on the other hand, are more commonly low grade (see below), and are often associated with plasma cell deciduitis (Figure 13.9) (see Chapter 14)[3]. Basal VUE has been associated with fetal/neonatal alloimmune thrombocytopenia[11][12], and, most recently, with morbidly adherent placentas (see Chapter 28)[14].

Grading

Grading of VUE is based on the number of contiguous involved villi. If the foci involve <10 contiguous villi, then the lesion is considered low grade; note that *at least 2 foci* are required to make this diagnosis. A low-grade VUE is further subdivided into "focal," if present on

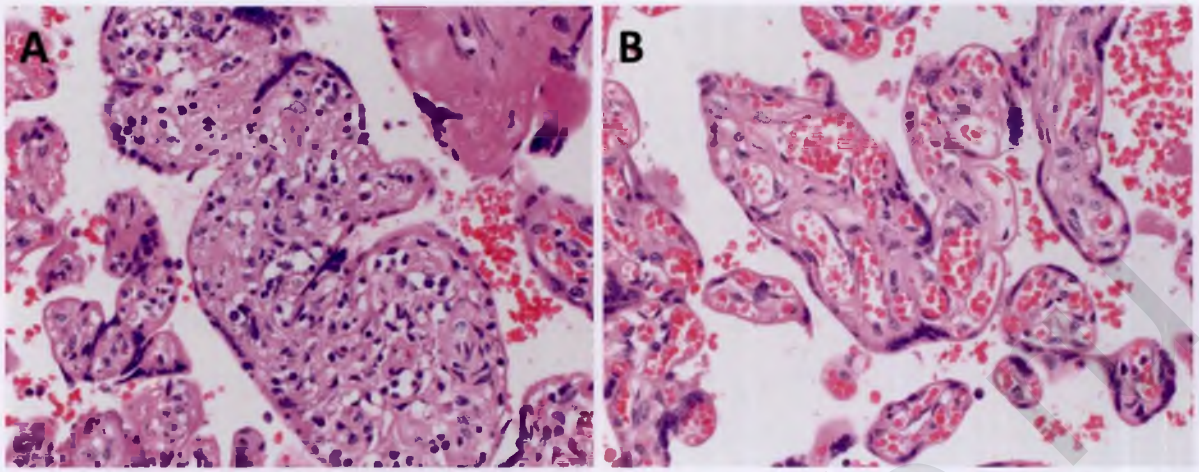

Figure 13.3 High-power view of villi involved with VUE (a) and normal villi (b) from the same case as shown in Figure 13.2.

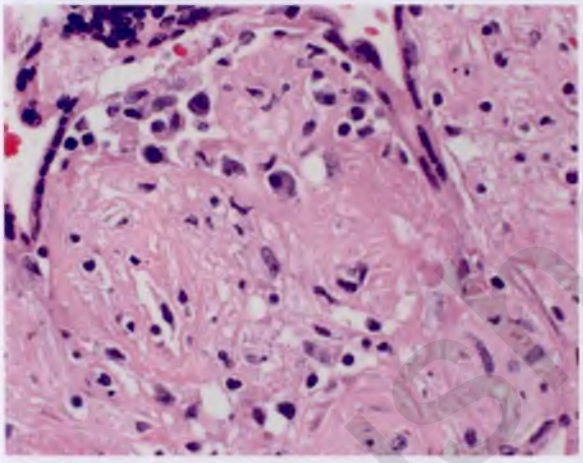

Figure 13.4 Example of a multifocal low-grade VUE with occasional plasma cells.

only 1 slide, and "multifocal," if present on 2 or more slides. If at least 1 focus involves 10 or more contiguous villi, the lesion is considered high grade. A high-grade VUE is further subdivided into "patchy" and "diffuse," with the latter defined as involving >30 percent of all distal villi[3]. High-grade VUE is more commonly associated with adverse perinatal outcomes, including IUGR, stillbirth, and long-term neurologic deficits in the newborn[3].

Commonly Associated Findings

Two lesions have been closely associated with VUE: *chronic chorioamnionitis and eosinophilic/T cell chorionic vasculitis* (see Chapter 14). Chronic chorioamnionitis consists of a primarily lymphocytic/mononuclear cell inflammatory infiltrate in the fetal membranes, often involving the choriodecidual boundary (Figure 13.10). Eosinophilic/T cell chorionic vasculitis is a lesion characterized by infiltration of fetal chorionic plate vessels by eosinophils and T cells, including Treg cells[15]. The significance of these lesions, by themselves, is not clear, although some studies have associated chronic chorioamnionitis with spontaneous preterm birth[16]. Nevertheless, the presence of either lesion should prompt the pathologist to look carefully for VUE. Both of these lesions are discussed in more detail in Chapter 14. *Plasma cell deciduitis (also known as lymphoplasmacytic deciduitis*, see Chapter 14), see Figure 13.9b, seen most often in association with the basal subtype of VUE, is diagnosed when groups of these cells are found to infiltrate the decidua. As the presence of plasma cells in the endometrial lining is also the definition of endometritis, it is thought that at least a subset of these basal VUE cases may be secondary to an underlying uterine infection. Therefore, particularly in cases of preterm delivery, we often comment on this finding in the pathology report and recommend follow-up testing and treatment for endometritis, if indicated. *Stem villous (or chorionic plate) vascular obliteration and associated avascular villi ("obliterative fetal vasculopathy")* is most commonly seen in subchorionic/midparenchymal VUE (see Figure 13.7b). In such cases inflammation of one or more fetal vessels leads to thrombosis and subsequent interruption of blood flow to terminal villi,

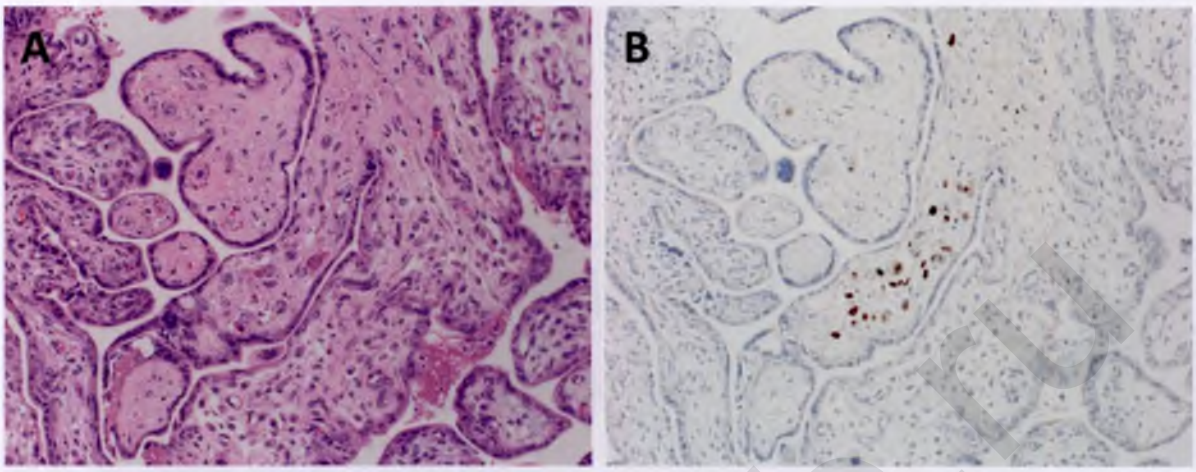

Figure 13.5 (a) Placenta of a 22-week fetus is infiltrated with plasma cells. (b) CMV infection is confirmed with immunohistochemical staining.

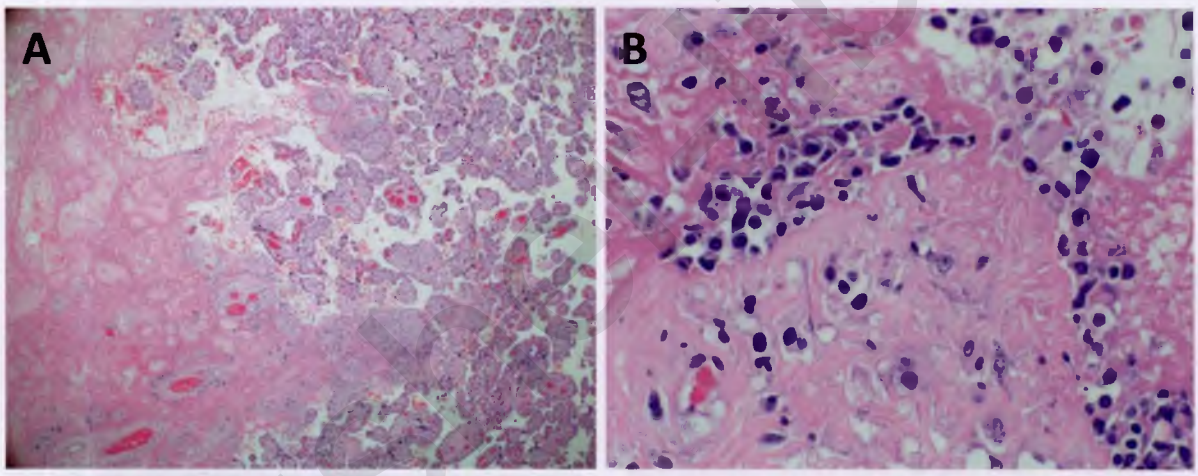

Figure 13.6 (a) Placenta of a severely growth-restricted baby, with confirmed maternal Zika virus exposure, showing extensive villitis association with infarction. (b) The inflammatory infiltrate included numerous plasma cells.

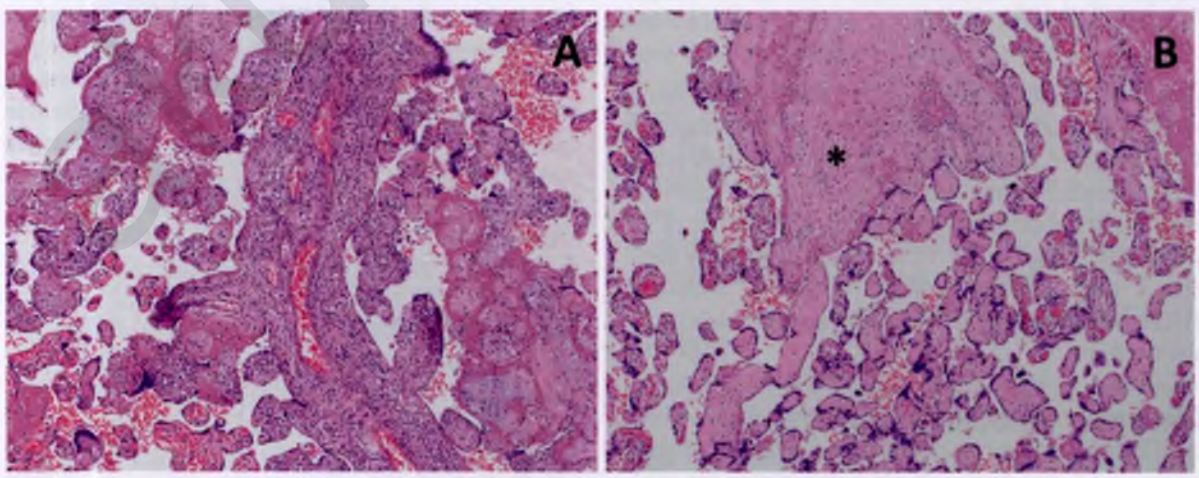

Figure 13.7 Involvement of stem villi with VUE, (a) without, or (b) with obliterative fetal vasculopathy. Note avascular villi surrounding the thrombosed fetal vessel (*).

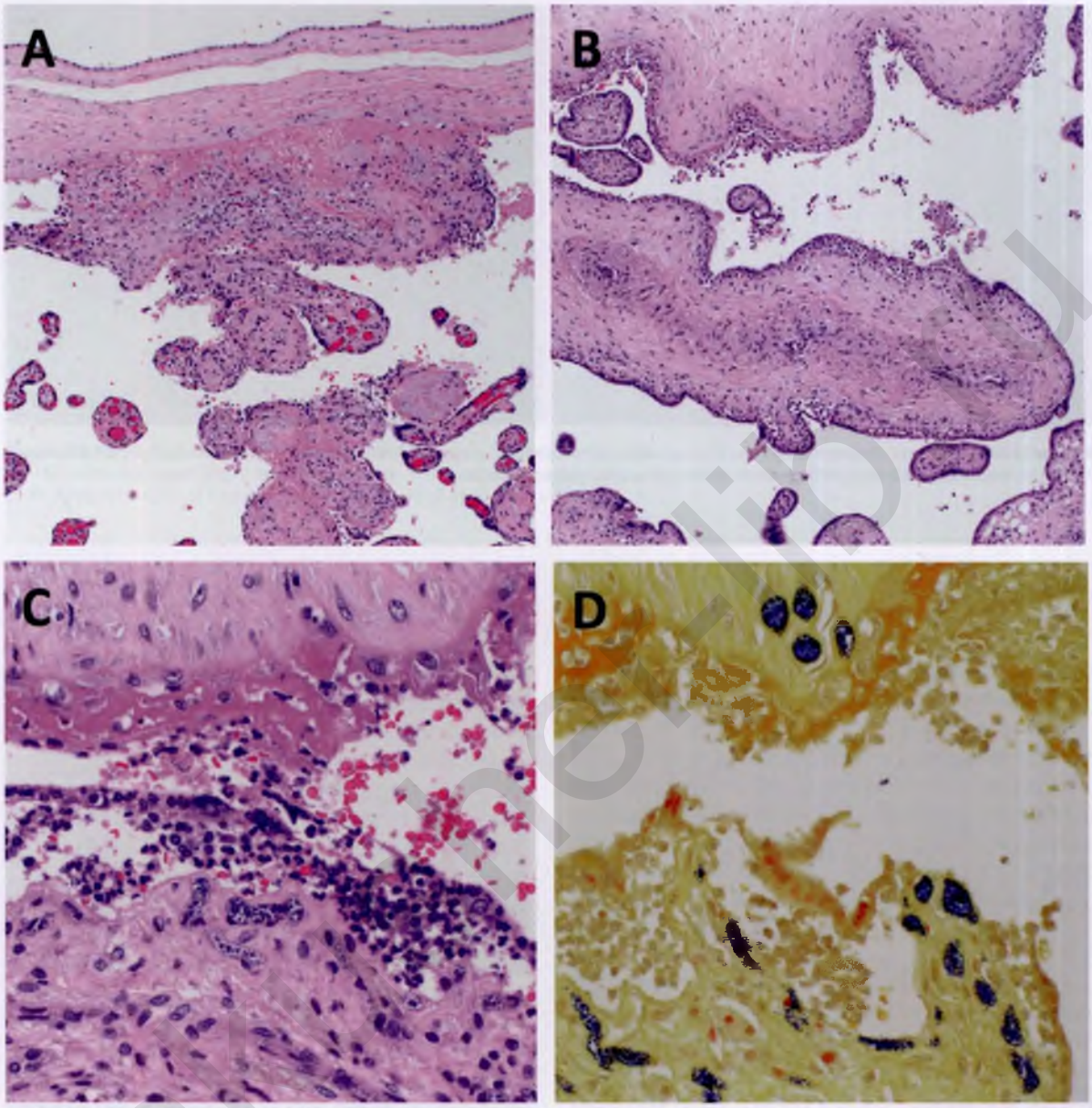

Figure 13.8 A case of subchorionic/midparenchymal villitis (a), with foci of dense neutrophilic infiltration (b, c); Gram-positive cocci were found to fill the fetal vessels (d). Cultures confirmed infection with group B Streptococcus.

eventually leading to loss of villous vascularity. VUE, in association with obliterative fetal vasculopathy, is more commonly associated with neurodevelopmental problems in the newborn, likely because of involvement of a larger proportion of chorionic villi, compared with VUE alone[17]. VUE can also be associated with *villous agglutination and infarction*, as well as with *perivillous fibrin deposition* (Figure 13.11), both of which contribute to a greater compromise of placental function and thus a higher risk of adverse perinatal outcomes. Cases with perivillous fibrin deposition can be associated with maternal autoimmune disease and are also more likely to recur[3][5].

Pitfalls/Differential Diagnosis

VUE should be distinguished from villitis of infectious etiology (see Chapter 12 and Figures 13.4–13.6).

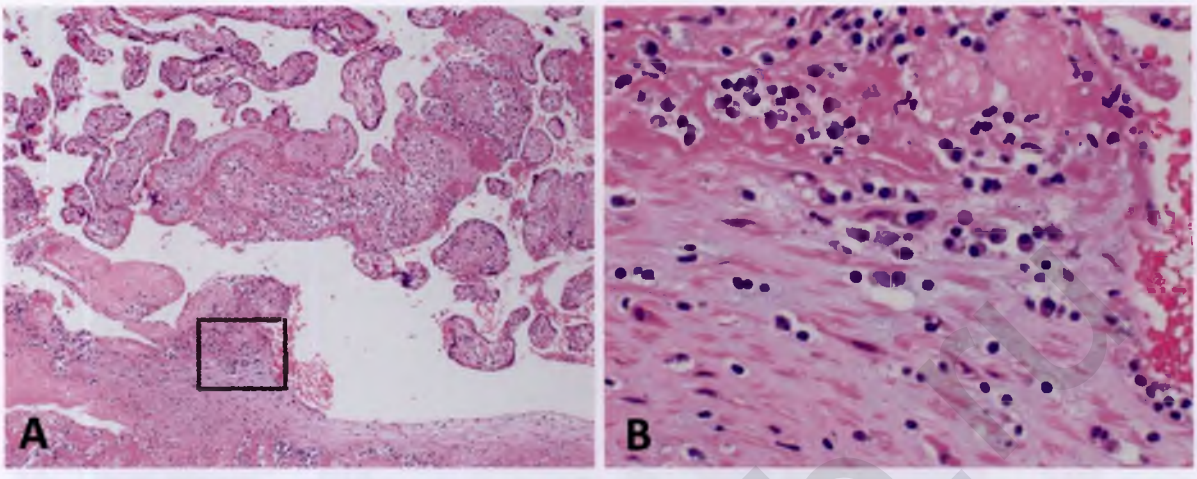

Figure 13.9 (a) A case of predominantly basal chronic villitis, with associated plasma cell deciduitis. (b) High-power view of indicated region in (a). This lesion was associated with preterm labor at 35 weeks gestational age.

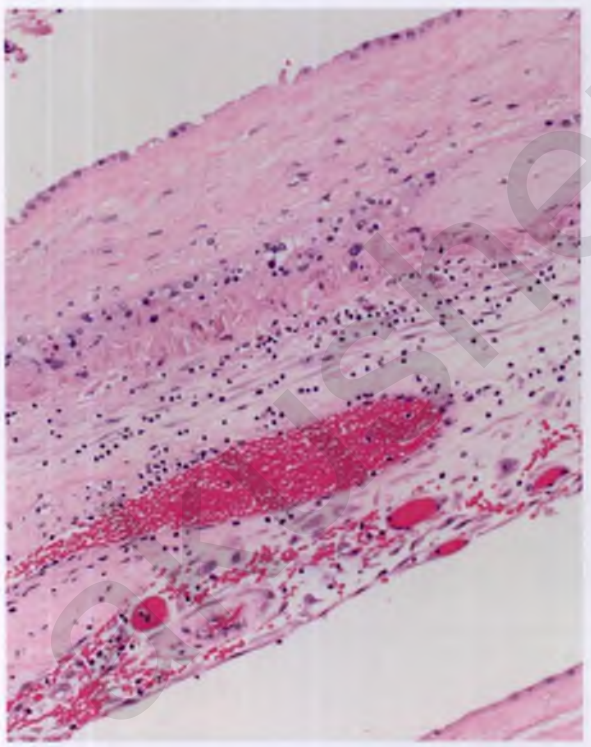

Figure 13.10 Chronic chorioamnionitis. A predominantly mononuclear inflammatory infiltrate involving the choriodecidua.

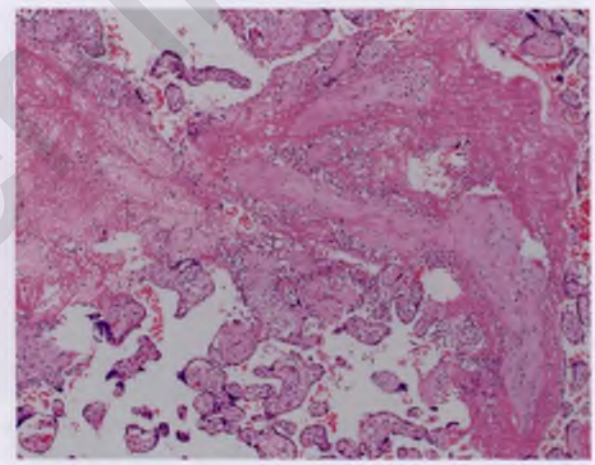

Figure 13.11 A case of diffuse VUE with associated perivillous fibrin deposition.

As explained above, the latter often includes a more prominent infiltration of villi by neutrophils, plasma cells, and/or (less commonly) granulomas, in addition to lymphocytes and macrophages. While a predominantly mononuclear, lymphohistiocytic infiltrate involving chorionic villi is relatively easily noted in a term placenta, it can be more difficult to pick up in late second trimester/early third trimester villi, which tend to have a more cellular stroma. Though it is rare to see VUE at this gestational age, if suspected, a CD3 immunostain highlighting T cells can easily identify this lesion (Figure 13.12). Fetal vascular malperfusion (FVM, see Chapters 33 and 34) is another lesion which needs to be distinguished from VUE, as FVM is most often associated with umbilical cord obstruction and is thus less likely to recur. Though completely avascular villi are easily distinguished from villi involved with VUE, villi which are incompletely

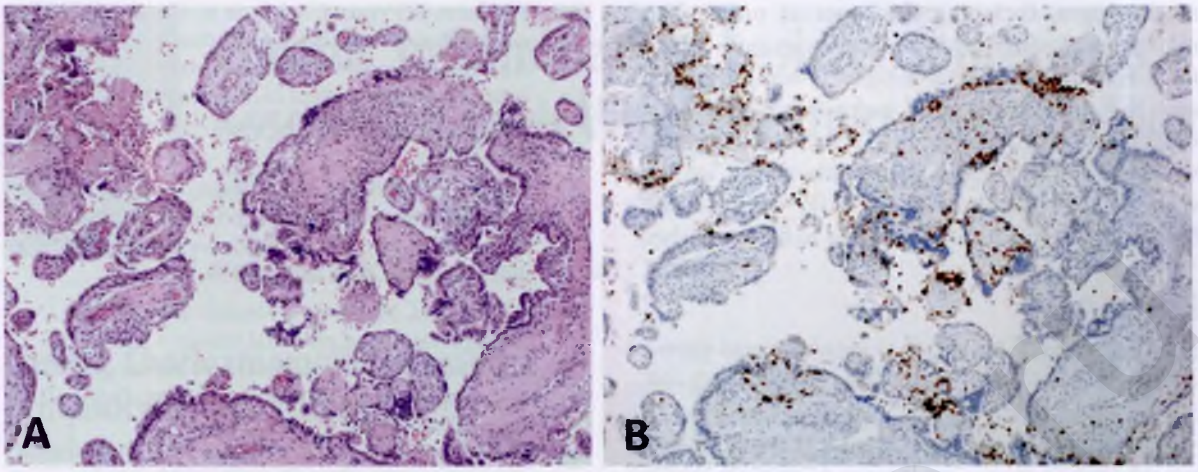

Figure 13.12 High-grade VUE in a second trimester placenta (a) confirmed by immunohistochemical staining for the pan T cell marker, CD3 (b). This lesion was associated with late miscarriage in the setting of an IVF pregnancy with a donor egg. Image provided with permission by M. Parast, University of California San Diego School of Medicine, La Jolla, CA.

avascular often contain karyorrhectic debris which can be mistaken for tissue necrosis associated with inflammation. In such cases, often a more careful evaluation of the lesion at high power can usually distinguish between the two lesions, although a CD3 immunostain may also be helpful. Of course, another caveat may be that the avascular villi indeed represent an area of "burnt-out" chronic villitis with loss of inflammatory cells. Finally, VUE should also be distinguished from chronic histiocytic intervillositis, a lesion where monocyte-macrophages fill the intervillous space and infiltrate perivillous regions. Although there may be some overlap in the pathogenesis of the two lesions[18], and they can even coexist in some cases[4], chronic intervillositis should be distinguished as it is not only associated with adverse perinatal outcomes, but also has a very high recurrence rate[4]. This lesion is discussed in more detail in Chapter 15.

Ancillary Diagnostic Testing: Typical cases of low-grade VUE do not require ancillary testing. If the lesion is high grade to diffuse, contains a significant neutrophilic or plasmacytic infiltrate, or if there are foci of necrosis or granuloma, an infectious etiology should be considered. A careful evaluation for presence of viral cytopathic changes, and special stains for bacterial and fungal microorganisms may be utilized, though, overall, they are not very high yield. Immunostaining (e.g. for CMV, HSV, or parvovirus) should not be performed routinely, but, when based on clinical suspicion of a specific infectious agent, may prove diagnostic (see Figure 13.5).

Prognostic Implications: High grade VUE is an important lesion to identify as it can recur in 10–15 percent of cases, often causing recurrent complications, including IUGR. When a high-grade lesion is associated with IUGR, particularly when the lesion is associated with perivillous fibrin deposition (as seen in Figure 13.1), a work-up for maternal autoimmune disease may be indicated. Low-grade VUE is often associated with a normal pregnancy, and is without clear prognostic implications.

Knowledge Gaps: Much remains to be discovered about VUE, including whether a proportion of cases are caused by as yet unidentified infectious agents. A study indicating an increased rate of VUE in placentas from HIV-positive women is provocative[19]. However, one study, using PCR for universal bacterial 16S rDNA, was unable to identify any such agent in 19 cases of multifocal VUE[20]. Still, more recent studies have reported VUE-like lesions in association with infection with papillomavirus[21] and influenza A[22]. As more sensitive molecular diagnostic tools become available, further attempts should be made at identifying, or ruling out, potential causative infectious agents, including viruses. At the same time, further study is needed regarding the mechanisms of fetal tolerance during pregnancy. These studies should include evaluation of the role of fetal versus maternal

macrophages, including the types of macrophages (M1/pro-inflammatory vs. M2/tolerogenic) involved, identification of the fetal antigen(s) being presented, and the mechanism(s) of recruitment, as well as the function(s), of maternal T cells. Furthermore, whether villous syncytiotrophoblast are involved early in the pathogenesis of VUE, or are simply bystanders in this disease, remains to be established.

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Chapter 14

Chronic Inflammatory Lesions Sometimes Associated with Villitis of Unknown Etiology (VUE)

Suzanne M. Jacques and Faisal Qureshi

Chronic Chorioamnionitis (Chronic Lymphocytic Chorioamnionitis)

Definition: Chronic chorioamnionitis is diagnosed in the presence of lymphocytic infiltration of the chorionic trophoblast layer or chorioamniotic membranes[1].

Clinical context: Chronic chorioamnionitis is a common histological placental lesion, and is frequently seen in association with both villitis of unknown etiology (VUE)[1–3] and chronic deciduitis[1,4]. Unlike VUE, which is largely a lesion of term placentas, chronic chorioamnionitis is more frequently seen in preterm placentas, having been reported in 14 percent of cases of term placentas with and without labor; 38 percent of cases of preterm placentas with preterm labor and intact membranes; and 36 percent of cases of preterm prelabor rupture of membranes[1]. Perhaps most significantly, it has been demonstrated to be the most common placental lesion of late-term spontaneous preterm delivery[1,5]. Chronic chorioamnionitis was also identified in 60 percent of placentas from a series of unexplained preterm fetal deaths[6].

Proposed Pathogenesis: As for VUE, evidence suggests that chronic chorioamnionitis is a histologically identifiable placental manifestation of maternal anti-fetal cellular rejection (allograft rejection), with the involved compartment in this lesion being the chorioamniotic membranes[1]. Although subclinical infection by microorganisms must be considered as an underlying etiology in some cases of chronic chorioamnionitis, studies of chronic chorioamnionitis have not demonstrated specific infectious agents[2,3]. The choriodecidual junction provides a large interface between maternal and fetal cells, which allows maternal immune cells in the decidua to recognize the chorionic trophoblasts (fetal cells), leading to inflammation at the choriodecidual junction in the event of an altered tolerogenic state[7].

That this lesion is a histologic manifestation of maternal anti-fetal rejection is supported not only by the association with VUE, but also associated dysregulation of T cell chemokines that have anti-angiogenic properties and are involved in the migration of CXCR3+ activated T lymphocytes[1]. Chemokine CXCL9, CXCL10, and CXCL11 mRNA expression is higher in the chorioamniotic membranes of placentas with chronic chorioamnionitis compared to controls, as is the median CXCL10 amniotic fluid concentration, suggesting a chemotactic gradient favoring migration of T cells from the decidua into the chorioamniotic membranes[1]. The finding of chronic chorioamnionitis also correlates with features of maternal anti-fetal antibody mediated rejection, including maternal anti-HLA antibodies shown to be specific against fetal HLA antigens, and Cd4 deposition[4,8]. Chronic chorioamnionitis is associated with a higher positive rate of maternal IgG class I and class II HLA panel reactive antibodies at delivery, and a higher seropositive conversion rate during pregnancy compared to controls[4]. Chronic chorioamnionitis is also associated with alterations of the amniotic fluid proteome, including increased T cell suppressor glyodelin-A concentrations, supporting a derangement of mechanisms governing maternal immune tolerance toward the fetus in its pathogenesis[9].

Gross Features: Chronic chorioamnionitis has no grossly identifiable features.

Microscopic Features: Chronic chorioamnionitis most frequently involves the free membranes but can also involve the membranes of the chorionic plate, the latter often occurring in the setting of chronic inflammation in other placental compartments (Figure 14.1). Most frequently the lymphocytic inflammation is seen at the choriodecidual border in the chorion laevae, frequently with only focal or minimal invasion into the trophoblastic layer (Figure 14.2 a, and b).

The inflammation is typically patchy, unlike acute chorioamnionitis, where the neutrophilic inflammation is typically diffuse. The lymphocytic infiltration can be accompanied by patchy trophoblastic necrosis, resulting from apoptosis, and leading to a "moth-eaten" appearance of the choriodecidual border[1].

Grading and staging of chronic chorioamnionitis has been proposed with stage 1 being lymphocytes limited to the chorionic trophoblast layer (Figure 14.2 a and b), stage 2 being the presence of lymphocytes in the chorioamniotic connective tissue (Figure 14.3 a and b), grade 1 being more than 2 foci of patchy inflammation, and grade 2 being diffuse inflammation. Increasing severity of inflammation has been shown to correlate with the amniotic fluid CXCL10 concentration[1].

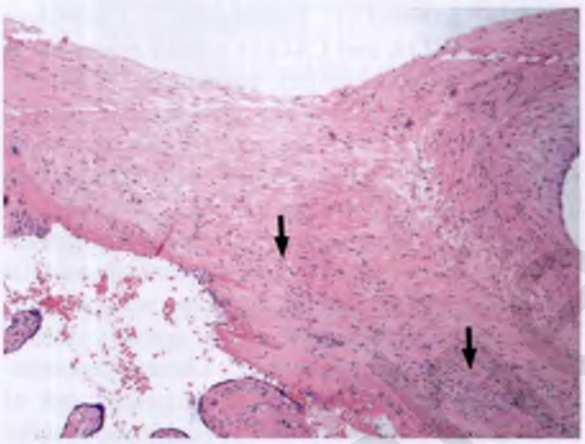

Figure 14.1 The membranes of the chorionic plate are infiltrated by mononuclear inflammatory cells (arrows).

Ancillary Diagnostic Testing: Immunohistochemical staining has shown that the lymphocytes are predominantly CD3+ or CD8+ T lymphocytes with smaller numbers of CD 4+ T lymphocytes; B cells are rare or absent[3]. While immunohistochemical staining for CD3 and CD8 will highlight the T lymphocytes in the membranes, this staining is generally not necessary for diagnosis.

Prognostic Implications: Chronic chorioamnionitis is significantly more frequent in preterm prelabor rupture of membranes and preterm labor/delivery when compared to term controls[1]. Studies have shown that chronic chorioamnionitis is a common placental pathology found in late preterm birth, suggesting that a major proportion of late preterm births may be due to maternal anti-fetal allograft rejection[1,5]. Chronic chorioamnionitis has been demonstrated to be more frequent in unexplained preterm fetal death when compared to live born controls, and this, along with the findings of higher amniotic fluid CXCL10 concentration and higher rate of maternal anti-HLA antibodies in the stillbirth cases, suggests that cellular and antibody-mediated anti-fetal rejection could be associated with fetal death in some cases (graft failure)[6].

Unlike solid organ transplants, which can be biopsied and examined for histologic features of ongoing rejection, it is not possible to serially biopsy the placenta or chorioamniotic membranes during

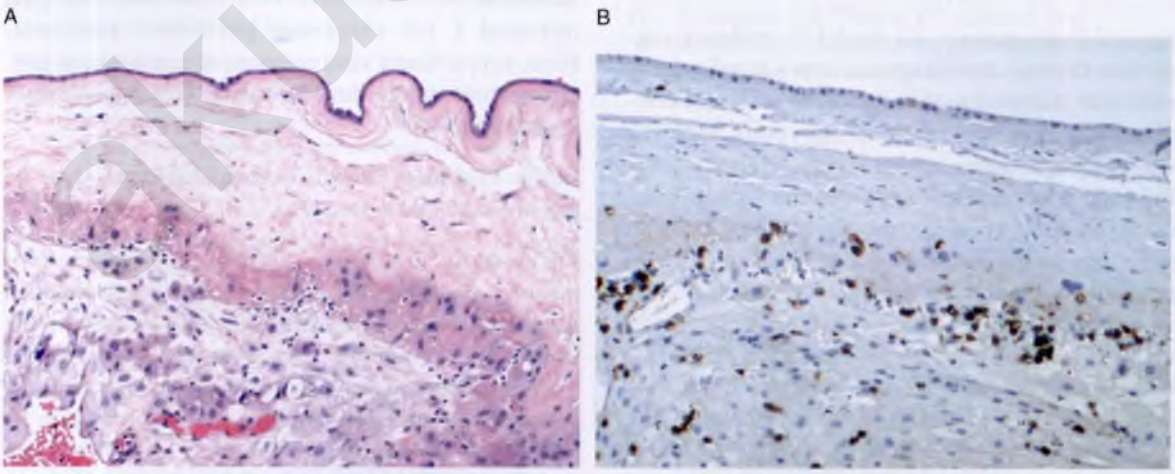

Figure 14.2 (a) Stage 1 chronic chorioamnionitis shows lymphocytes at the choriodecidual border with infiltration into the chorionic trophoblast layer, but sparing the chorioamniotic connective tissue. (b) Immunohistochemical staining for CD8 highlights the cytotoxic CD8+ T lymphocytes limited to the choriodecidual interface.

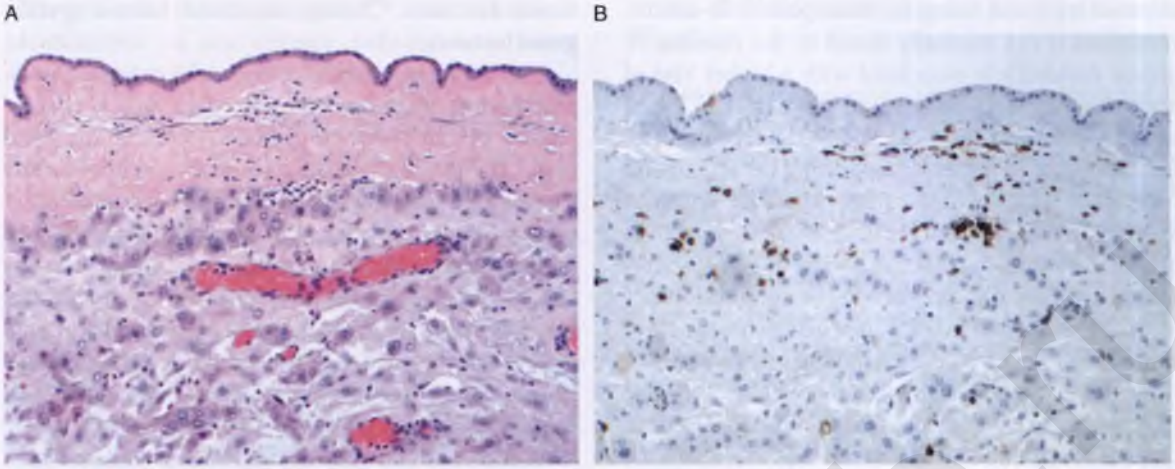

Figure 14.3 (a) Stage 2 chronic chorioamnionitis with lymphocytes within the chorioamniotic connective tissue. (b) Immunohistochemical staining for CD8 highlights the cytotoxic CD8+ T lymphocytes extending into the chorioamniotic connective tissue.

pregnancy. This limits the usefulness of chronic chorioamnionitis in the identification and monitoring of anti-fetal rejection; however, it has been proposed that HLA-panel reactive antibodies, which correlate with the finding of chronic chorioamnionitis, may be useful as a monitoring tool of maternal humoral anti-fetal rejection and fetal well-being, but this is not yet being used in clinical practice[4].

Knowledge Gaps: Further studies are needed to clarify the association of chronic chorioamnionitis with cellular and antibody-mediated anti-fetal immune repsonses and adverse pregnancy outcome, particularly late-term prematurity, as well as the mechanisms whereby this response leads to adverse outcomes. Although it is currently possible to screen for maternal antibodies against fetal HLA, further investigation is needed to implement effective diagnosis and management of pathologic maternal anti-fetal immune responses during pregnancy[7]. The recurrence rate of chronic chorioamnionitis in subsequent pregnancies is not known.

Chronic Deciduitis (Lymphoplasmacytic Deciduitis; Chronic Lymphoplasmacytic Deciduitis; Chronic Deciduitis with Plasma Cells)

Definition: Chronic deciduitis is defined as the presence of plasma cells in a background of lymphocytic inflammation in the decidua of the basal plate, including focal lymphocytic inflammation (lymphoplasmacytic deciduitis)[10]. Chronic deciduitis can also be diagnosed in the absence of plasma cells if there is a diffuse lymphocytic infiltrate in the basal plate[10]. Most investigators reporting on chronic deciduitis require the presence of plasma cells for diagnosis, and the significance of chronic deciduitis without plasma cells may not be the same.

Clinical Context: Chronic deciduitis is a common finding, and is seen more frequently in preterm compared to term placentas, having been reported in 8–25 percent of preterm placentas and 2–13 percent of term placentas[1,11]. Chronic deciduitis is frequent in spontaneous abortion, having been reported in 9–20 percent in chromosomally normal spontaneous abortion, and 4–30 percent chromosomally abnormal spontaneous abortion[12,13]. It has been reported to be particularly frequent in patients with recurrent chromosomally normal spontaneous abortion (25 percent)[12]. In contrast, it has a reported frequency of 0 percent in elective abortion[13]. Chronic deciduitis is frequently seen with VUE and chronic chorioamnionitis, but can be seen in isolation[1]. It is very frequently seen with basal villitis[1,14].

Proposed Pathogenesis: Chronic deciduitis may be the result of microbial colonization of the endometrium or pelvic inflammatory disease; however, its association with VUE and chronic chorioamnionitis suggests that in many cases it represents a histological manifestation of maternal anti-fetal rejection, with the involved placental compartment in this chronic

inflammatory lesion being the basal plate[7]. B-cell differentiation is not normally found in the decidua[15]. Chronic deciduitis is associated with a higher rate of maternal serum IgG class I and class II HLA panel reactive antibodies[4] and placental Cd4 deposition[13] when compared to controls, supporting the association of decidual plasma cells with maternal immune response to fetal antigens, rather than to infection. Chronic deciduitis has been reported to be more frequent in egg donation pregnancies (embryo immunogenetically unrelated to the mother), compared to nondonor in vitro fertilization pregnancies (semiallografts), also suggesting an immune origin[16,17]. The higher frequency of chronic deciduitis reported in recurrent abortion may be related to repeated maternal exposure to fetal antigens.

Gross Features: Chronic deciduitis has no specific gross features.

Microscopic Features: Chronic deciduitis is characterized by the presence of plasma cells in the basal plate. The plasma cells are usually sparse, but in some cases are diffuse, and they are usually accompanied by increased lymphocytes. Lymphocytic inflammation in the absence of plasma cells can be diagnosed as chronic deciduitis if the infiltrate is diffuse, but careful inspection will frequently reveal at least rare plasma cells in the presence of diffuse lymphocytic inflammation. Chronic deciduitis is frequently seen with VUE, and basal chronic villitis is particularly likely to be associated with chronic deciduitis (Figure 14.4 a and b)[14,18]. Chronic deciduitis is also frequently seen

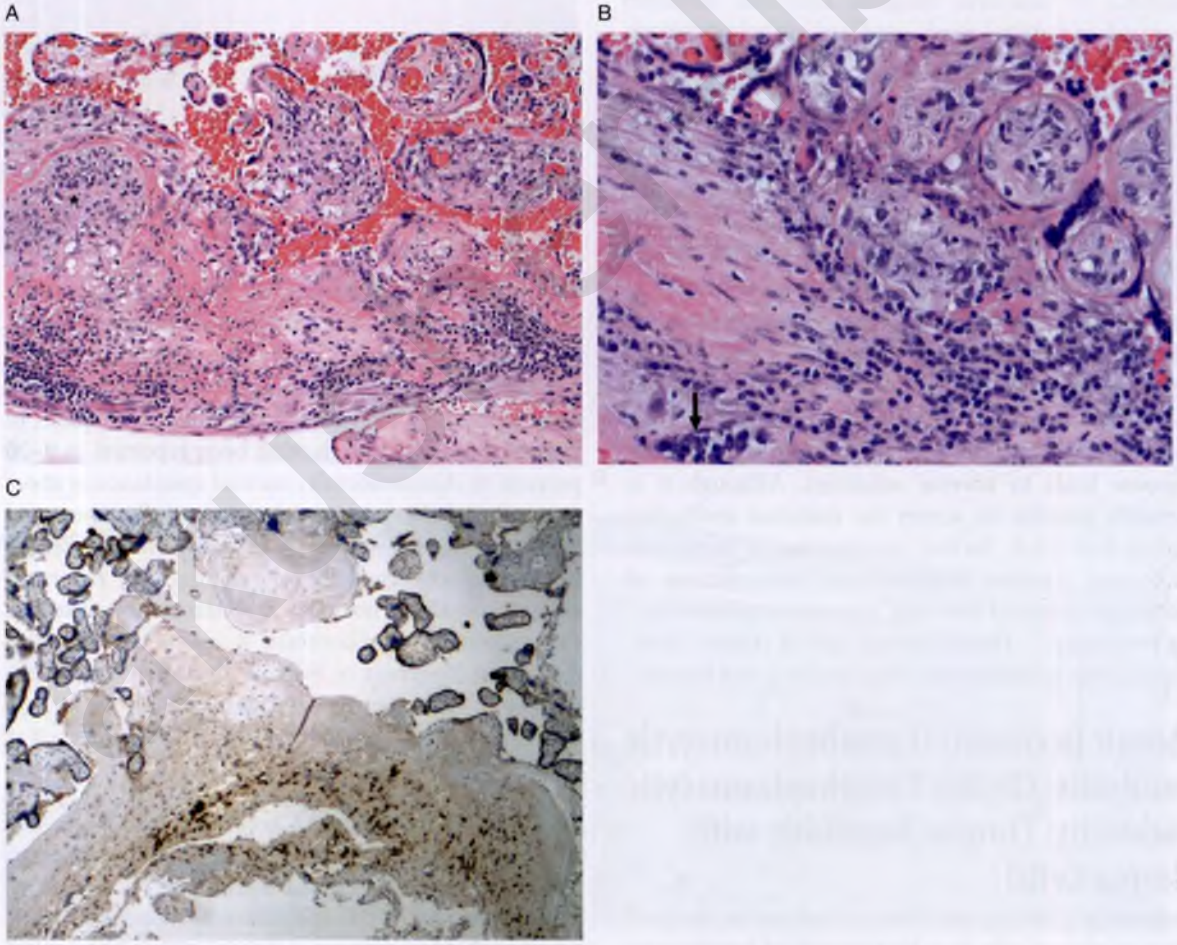

Figure 14.4 (a) Chronic deciduitis with dense infiltration of the basal plate by plasma cells and lymphocytes and with basal villitis involving adjacent anchoring villi (asterisk). (b) Plasma cells, including in small clusters (arrow) are seen in this dense chronic inflammatory infiltrate in the basal plate. (c) Immunohistochemical staining for CD138 highlights the plasma cells.

with chronic chorioamnionitis[2,4], and therefore identification of one chronic inflammatory lesion should elicit careful search for the others.

Ancillary Diagnostic Testing: Immunohistochemical staining for CD138 will confirm the presence of plasma cells (Figure 14.4c).

Prognostic Implications: Chronic deciduitis is associated with preterm labor[1,19]. Chronic deciduitis is also frequently found in both chromosomally normal and chromosomally abnormal spontaneous abortion, with some investigators reporting a higher frequency of chronic deciduitis in chromosomally normal compared to chromosomally abnormal spontaneous abortion[12], while others did not find this association[13]. Chronic deciduitis has been shown to be frequently associated with placental C4d deposition in spontaneous abortion, a feature of the classical complement activation, and this has been proposed as a common mechanism of placental and fetal injury[13].

Knowledge Gaps: The antigenic stimulus eliciting the lymphoplasmacytic inflammation is not known, nor is the reason why chronic inflammatory lesions occur in different placental compartments, frequently with other chronic inflammatory lesions, but also often in isolation. While current evidence suggests that chronic deciduitis in many cases is a histological manifestation of maternal anti-fetal rejection, its association with preterm labor and spontaneous abortion require further investigation, as do the mechanisms by which it leads to placental injury in these adverse outcomes.

Eosinophilic / T Cell Chorionic Vasculitis

Definition: Eosinophilic/T cell chorionic vasculitis (E/TCV) is a lesion in which fetally derived inflammatory cells, predominantly eosinophils and CD3+ lymphocytes, involve large fetal blood vessels, usually a single chorionic surface blood vessel[20,21].

Clinical Context: E/TCV is an unusual lesion with reported frequency ranging from 0.37 percent to 0.6 percent in placentas examined[20,21]. E/TCV is found most frequently in term placentas[21,22], as is VUE, but it has been reported as early as 23 3/7 weeks[23]. VUE is a frequent association with E/TCV (32 percent to 43 percent of cases of E/TCV))[21,22]. Intravascular thrombi are also frequently seen with E/TCV (26–43 percent of E/TCV cases)[21,22]. No consistent associated maternal of fetal clinical conditions or characteristics have been identified.

Proposed Pathogenesis: Although the term for this lesion includes the word "vasculitis," suggesting an inflammatory reaction directed at the vascular wall, the lack of vascular necrosis and extension of inflammatory cells outside the vessel wall do not support this. The focal nature of the inflammation originally led to the suggestion that it is a response to focal vascular injury[20]. Because the inflammatory infiltrate can be facing toward or away from the amniotic cavity, or involve the entire circumference of the blood vessel, it is not believed to be a response to a process within the amniotic cavity; but the location and nature of the inciting stimulus remain obscure[21]. The association with intravascular thrombi suggests that the thrombi may be forming as the result of injury to the vessel, possibly caused by the inflammation. Alternatively the inflammation could be a response to the formation of the thrombus[21].

The fetal origin of the inflammatory cells in E/TCV has been confirmed by fluorescence in situ hybridization (FISH)[24]. Immunohistochemical staining shows the lymphocytes to be predominantly T cells (CD3, CD4 and CD8 positive), but some cases also include B lymphocytes (CD20 positive)[21,22]. FOXP3+ and CD25+ regulatory T cells are a significant subpopulation (20–26 percent) of the of T cell population, possibly serving to modulate the inflammation[22]. The infiltrate also includes CD68 positive monocyte-macrophages[21,22]. The reason for the association of E/TCV of fetal origin with VUE, a lesion with maternally derived T lymphocytes and features of maternal anti-fetal rejection, is not known.

Gross Features: E/TCV has no typical gross findings. The frequently associated intravascular thrombi may be visible grossly if large or occlusive, but in most cases these thrombi are microscopic findings.

Microscopic Features: The inflammatory cells in E/TCV migrate from fetal blood vessels, and the mixed infiltrate is composed predominantly of eosinophils and lymphocytes, but also includes macrophages (Figure 14.5 a and b). E/TCV is limited to a single chorionic surface blood vessel in most cases, but it can be multifocal, and also can involve the stem villous vasculature[21]. The inflammation involves less than half the circumference of the blood vessel in a majority of cases, but the inflammation can be

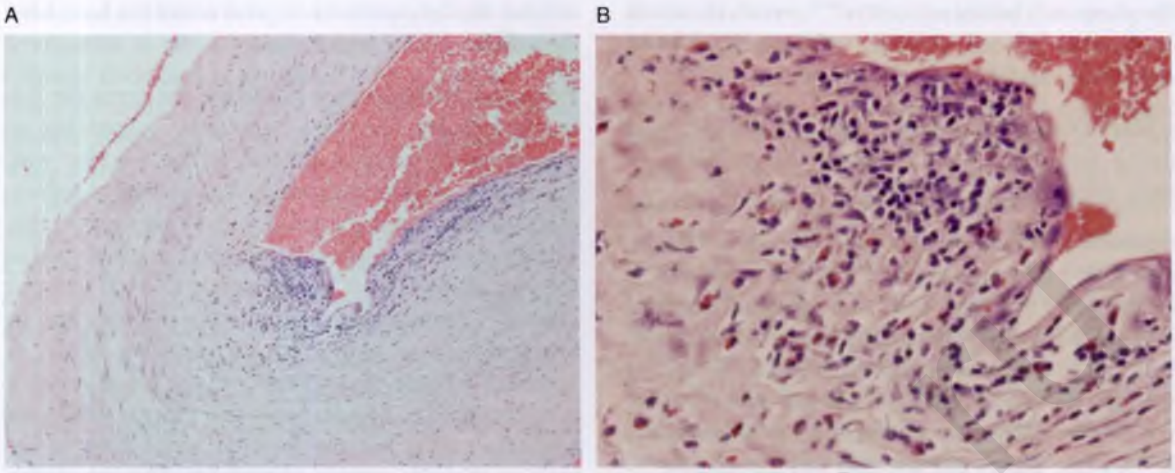

Figure 14.5 (a) Eosinophilic/T cell chorionic vasculitis (E/TCV) with the inflammatory infiltrate within the muscular wall of the chorionic surface blood vessel facing toward the intervillous space. The inflammatory infiltrate involves approximately 50 percent of the circumference of the blood vessel. (b) The inflammatory infiltrate is composed predominantly of lymphocytes and eosinophils.

circumferential and can radiate toward or away from the amniotic cavity[21]. Microscopic mural or intramural thrombi are associated with E/TCV and can be seen either at or away from the focus of E/TCV[21].

Ancillary Diagnostic Testing: Immunohistochemical staining for CD3 will confirm the presence of lymphocytes, but this is generally not necessary for diagnosis.

Prognostic Implications: No consistent maternal or fetal medical conditions or adverse fetal outcomes have been associated with E/TCV.

Knowledge Gaps: Unanswered questions regarding this poorly understood entity include the nature of the stimulus eliciting this inflammation, the nature of the relationship with VUE and intravascular thrombi, and whether this lesion has the potential for recurrence.

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Chapter 15

Chronic Histiocytic Intervillositis

Raymond W. Redline

Chronic Histiocytic Intervillositis (Massive Chronic Intervillositis, Chronic Intervillositis of Unknown Etiology, Massive Perivillous Histiocytosis, Mixed Chronic Histiocytic Intervillositis-Increased Perivillous Fibrin Deposition)

Definition: Patchy to diffuse infiltration of the intervillous space by a monomorphic population of monocyte macrophages without a significant component of chronic villitis.

Clinical Context: Chronic histiocytic intervillositis (CHI) is a rare idiopathic chronic inflammatory process affecting up to 4.4 percent of all first trimester miscarriages and 0.6 percent of second and third trimester placentas submitted to pathology[1,2]. Its prevalence is much higher with chromosomally normal recurrent miscarriage (31 percent in one study)[3]. Overall recurrence rate ranges from 67–100 percent without treatment in most studies, and patients with recurrence can present at any stage of pregnancy[2]. There is a strong association with maternal autoantibodies or autoimmune disease[4,5]. Individual reports and larger studies have also documented associations with neonatal alloimmune thrombocytopenia, artificial reproductive technology, and cytomegalovirus infection[6–9]. Affected pregnancies delivering after 22 weeks have a high rate of fetal growth restriction (62 percent) and stillbirth (46 percent), and only rare cases reach term[10]. Elevated maternal serum placental alkaline phosphatase is under study as a biomarker for disease (see below). A very recent study encompassing all cases from a single large perinatal center over a 13-year time period added some additional useful information, including a strong associations with clinical preeclampsia (27 percent), histologic maternal vascular malperfusion (24 percent), and abnormal antenatal biochemical screening for aneuploidy (low first trimester PAPP-A in 50 percent of cases and elevated second trimester Inhibin-A in 25 percent of cases)[11]. Treatment of patients with recurrent CHI has employed in decreasing order of frequency one or more of the following agents: aspirin, corticosteroids, low molecular weight heparin, and hydroxychloroquine. In a small series, these therapies resulted in a significant decrease in recurrence[5].

Proposed Pathogenesis: Maternal inflammatory cells, approximately 80 percent CD68-positive monocyte macrophages and 20 percent T lymphocytes with an equal CD4/CD8 ratio, accumulate within the intervillous space, often in contact with the surface of syncytiotrophoblast[12]. Syncytiotrophoblast in affected placentas also shows upregulation of ICAM-1 adhesion molecules and TLR1 pattern recognition receptors[13,14]. High numbers of maternal anti-paternal CD8 cytotoxic lymphocyte precursors are found in 75 percent of cases, and most women have circulating anti-paternal HLA antibodies[15]. Gene expression profiling shows distinct differences from both normal placentas and those with the chronic villitis[16]. The latter show increased expression of T cell chemokine and metalloproteinase inhibitor TIMP-1 genes, while CHI shows elevated metalloproteinase MMP9 and TGF beta receptor 1 gene expression. There is also an increased number of T regulatory cells in both the intervillous space and decidua basalis of CHI cases[12]. Development of CHI in any given placenta appears to be context dependent in that discordancy for CHI has been observed in monochorionic twins[17]. CHI bears strong similarities to the massive chronic intervillositis seen in some cases of malaria (see below and Chapter 11), where an immune response to falciparum malarial parasites that adhere to the apical surface of syncytiotrophoblast has been documented[18–20]. Taken together, the above evidence suggests that CHI represents an adaptive immune response to antigens, possibly paternally derived, on the trophoblastic surface occurring most commonly in

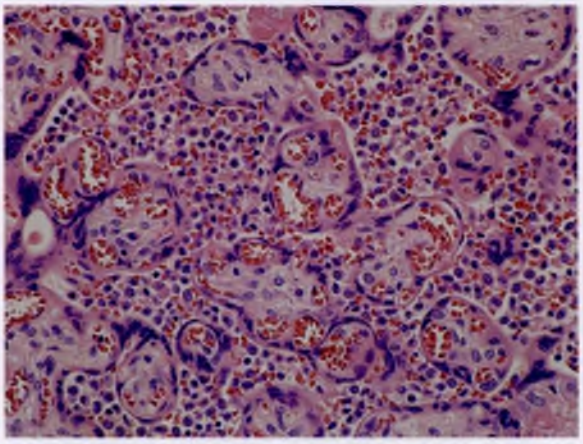

Figure 15.1 Chronic histiocytic intervillositis. Dense monomorphic infiltrate of monocyte macrophages confined to the intervillous space around otherwise unremarkable distal villi.

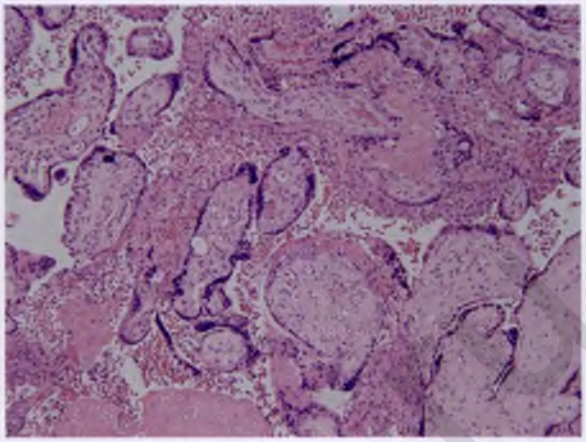

Figure 15.2 Mixed chronic intervillositis and increased perivillous fibrin(oid). Patchy intervillous infiltrate of fibrin(oid) and monocyte macrophages adherent to, but not invading, the distal villi.

women with an underlying predisposition to form autoantibodies.

Gross Features: Placentas are often small and thin with decreased weight for gestational age. Patchy-diffuse firmness on cut section due to associated perivillous fibrin(oid) may be seen in some cases.

Microscopic Features: Abnormalities are confined to the intervillous space. A dense patchy-diffuse infiltrate of monomorphic monocyte macrophages with typical uniform bean-shaped nuclei fills the intervillous space in multiple regions of the placenta (Figure 15.1). Rarely, more localized or mild involvement may be observed (<20 percent of intervillous space involved), especially in treated cases[12]. Individual monocyte macrophages are often clumped together, sometimes adherent to the surface of the villous trophoblast, and a variable amount of perivillous fibrin(oid) is often present. Exceptionally, the amount of fibrinoid overlaps with that seen with maternal floor infarction/massive perivillous fibrin deposition (see Chapter 17), which has a similarly high perinatal mortality and recurrence rate (Figure 15.2)[21]. However, any lesion with a significant component of intervillositis should be classified under CHI. Importantly, cases of chronic villitis may also have a significant component of intervillositis (see Chapter 13), but the nature of the intervillous infiltrate is more polymorphous with a mixture of activated macrophages and other inflammatory cells. Only rare foci of chronic villitis, generally away from the intervillous infiltrate are compatible with a diagnosis of CHI. CHI overlaps histologically with massive chronic intervillositis, a lesion seen in some patients with new onset falciparum malaria infection during pregnancy (see Chapter 12). Malarial placentas generally show more fibrin intermixed with black hematozoin pigment, necrotic debris, occasional neutrophils, and rare trophozoites in RBC. More than an occasional neutrophil in the intervillous infiltrate should raise the possibility of infections such as listeriosis, maternal sepsis, or other rare infections such as rickettsia, psittacosis, coccidiomycosis, and some viruses (see Chapter 11).

Ancillary Diagnostic Testing: Immunohistochemical staining for CD68 can be used to document the lineage of the intervillous monocyte/macrophage infiltrate (Figure 15.3). Mean density of CD68-positive cells in cases was at 88 + 23/HPF compared to 8 + 5/HPF amongst controls in one study[22]. As mentioned above, more than fivefold elevations in maternal serum alkaline phosphatase have been documented in over half of CHI cases[10,23].

Prognostic Implications: Overall perinatal mortality rate for CHI is 80 percent[24]. Surviving infants are often compromised by extreme prematurity, FGR, and depressed status at birth. As in other cases of marked FGR, affected infants may show severe osteopenia and altered bone growth. Mothers often suffer from recurrent miscarriages or pregnancy losses at all gestational ages. Immune-

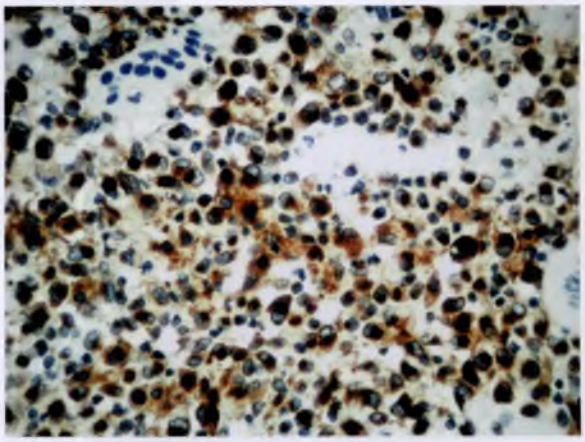

Figure 15.3 CD68-positive monocyte macrophages within the intervillous space in chronic histiocytic intervillositis (CD68 immunostain).

directed therapies can decrease the recurrence rate by up to 50 percent.

Knowledge Gaps: The extreme rarity of cases poses significant challenges for study of CHI. The identity of the antigenic stimulus (i.e. maternal autoantigen, trophoblast specific antigen, or paternal alloantigen) is unknown. Recurrence and evidence of T cell immunity, as detailed above, suggest an adaptive immune response. Whether there are differences in pathogenesis between cases of varying severity, presentations at differing stages of pregnancy, or recurrent and nonrecurrent cases is unclear. Specificity for a given partner, possible genetic predisposition, and optimal therapy are additional outstanding questions. An NIH-registered clinical trial using alkaline phosphatase as a biomarker for CHI promises to add significantly to our understanding of this rare but devastating disease[23].

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Chapter 16

Placental Size, Shape, and Umbilical Cord Abnormalities

Raymond W. Redline

The prototypical normal human placenta is implanted in the anterior or posterior fundic portion of the uterus. It has a regular contour, and is slightly ovoid with a longer rostral-caudal axis (length) than lateral axis (breadth) relative to the uterus. The umbilical cord insertion site is usually paracentral[1,2]. Placental weight (PW) relative to fetal weight (FW) normally follows an allometric formula ($PW = 1.03 \times FW^{0.75}$)[3]. Both surface area (roughly estimated by ellipse formula, length x width x $\pi/4$) and thickness increase proportionally with increasing placental weight[4]. Variations from these ideal characteristics are significant determinants of birth weight and possibly of adverse short and long term pregnancy outcomes. Placental weight alone accounted for 37 percent of the variance in birth weight in the Collaborative Perinatal Project dataset of over 36,000 pregnancies with available placental measurements[5]. Lateral dimensions, thickness, shape, and umbilical cord insertion site together contributed an additional 28 percent, while clinical risk factors accounted for only 14 percent of the variance. Recent studies have shown that variations from the normal placental configuration are determined at an early stage and can be detected by ultrasound as early as 10–14 weeks of pregnancy[6]. While gross abnormalities can in part be caused by the histologic patterns of placental injury discussed elsewhere in this volume, they should be given separate weight when formulating a final interpretation and included in the pathology report. Appendix 9 provides the means and standard deviations of various gross measurements for placentas submitted to pathology over the past 10 years at University Hospital Cleveland Medical Center.

PLACENTAL SIZE

Abnormal Weight and/or Fetoplacental Weight Ratio

Definition: A trimmed placental weight (after removal of membranes and umbilical cord) falling outside of the tenth to ninetieth percentile range for gestational age (GA) using the best available population specific standards. Since the placenta is a fetal organ, there is a relatively constant relationship between fetal and placental weights for GA in normal cases (see above formula). Deviation from expected, i.e. an abnormal, fetoplacental weight ratio (FPR = fetal weight/ placental weight) for GA, can provide useful diagnostic information.

Clinical Context: Small for gestational age (SGA) placentas are often associated with fetal growth restriction (FGR). FGR with placental weight less than the third percentile and an increased FPR is most frequent with preterm preeclampsia, but can also be seen in normotensive pregnancies with underlying maternal vascular disease (chronic hypertension, thrombophilia, collagen vascular disease, renal disorders), chronic villitis associated with congenital infections, and genetic/chromosomal abnormalities including confined placental mosaicism[7–9]. Constitutionally small infants without FGR and infants with FGR due to other causes, such as antenatal corticosteroid treatment, usually have proportionally small placentas (normal FPR), while FGR associated with maternal smoking and artificial reproductive technology is often accompanied by a decreased FPR[10–12]. Large for gestational age (LGA) placentas are associated with fetal macrosomia. Macrosomia with fetal weight greater than the ninety-seventh percentile and a decreased FPR is most common with poorly controlled maternal diabetes, but it can also be seen with maternal obesity or anemia, fetal hydrops or metabolic storage disease, and fetoplacental overgrowth syndromes (e.g. Beckwith-Wiedemann (BWS), Smith-Golabi-Behmel, and Proteus syndromes)[7,8,12–15]. Constitutionally large infants, including those associated with excessive maternal pregnancy weight gain, tend to have symmetrically enlarged placentas and a normal FPR. Placentas from macrosomic infants with preeclampsia at term, long-standing maternal diabetes, or chronic hypertension can even have an increased FPR[16].

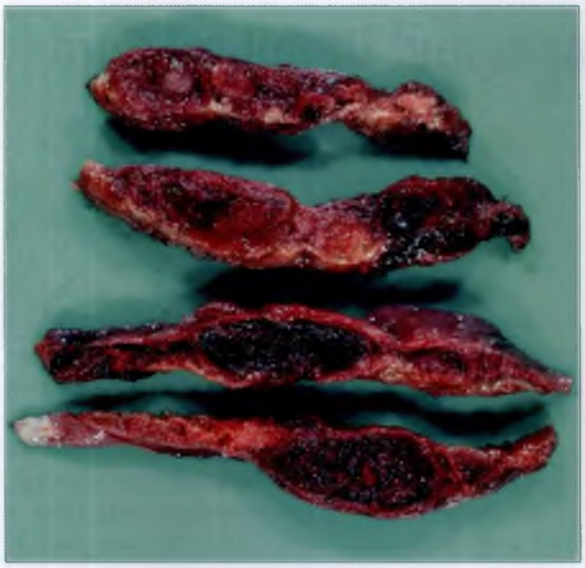

Figure 16.1 Small for gestational age placenta from growth-restricted infant. Cross sections also show irregular thickness with marginal atrophy (bottom left) and multiple villous infarcts (top two sections).

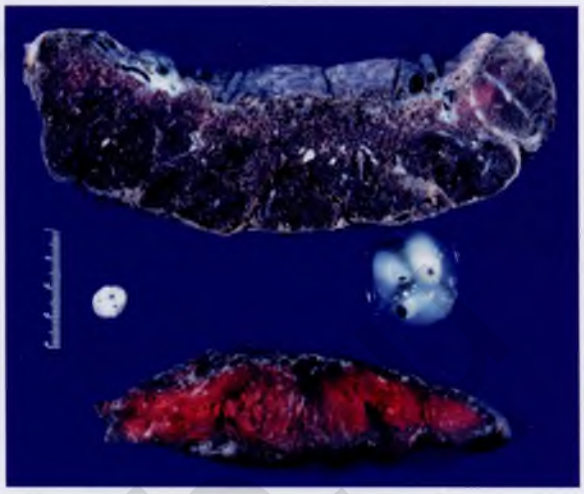

Figure 16.2 Large for gestational age placenta from macrosomic infant. Single cross section (top) shows symmetric, uniform expansion of the width and thickness of placental parenchyma plus a thick umbilical cord. A normal weight, term placenta with unremarkable umbilical cord processed the same day is at the bottom for comparison.

FPR has been considered by some to be a proxy for "placental efficiency" or even fetoplacental basal metabolic rate[17]. However, a word of caution is in order. While FPR may be a good metric for efficiency across species or at varying stages of gestation in the same species, it can be confounded in pathologic states by varying amounts of damaged nonfunctioning placental parenchyma, tissue edema, and supportive fibrous stroma, making it less specific in these contexts. Additional findings of interest are (1) that even with fetal and placental weights in the normal range, a decreased FPR is associated with prepregnancy obesity, poor gestational weight gain, and low Apgar scores; and (2) that FPR shows sexual dimorphism, tending to increase with increasing birth weight for female infants but remaining constant for males[18,19].

Proposed pathogenesis: An SGA placenta with an increased FPR usually indicates either (1) inappropriately reduced growth due to maternal malperfusion, malnutrition, or genetic/chromosomal factors; or (2) placental damage due to premature separation, infection, maternal immune attack, or fetoplacental thrombosis[7,20,21].

The pathogenesis of LGA placentas can be separated into 3 categories: (1) accelerated normal growth due to an increased supply of nutrients (e.g. excessive maternal pregnancy weight gain); (2) an excess of placental growth factors (e.g. insulin, IGF2, Peg3, MEST) relative to growth factor inhibitors (e.g. H19, p57), seen with diabetes or epigenetic/ genetic imprinting disorders such as BWS (see Chapter 9); and (3) excessive accumulation of extracellular substances (e.g. edema fluid in hydrops fetalis or mucopolysaccharides in metabolic storage disease; see Chapters 11 and 24)[7,8,14,22,23].

Gross Features: SGA placentas often show additional gross structural abnormalities, as discussed below, including reduced chorionic diameter, irregular thickness, irregular peripheral contour, elongated shape (increased maximum minus minimum diameter), and a thin umbilical cord (Figure 16.1). LGA placentas tend to be otherwise normal with symmetric increases in length, width, and thickness and, often, an increased umbilical cord diameter (Figure 16.2).

Microscopic Features: Many SGA placentas with an increased FPR show histologic features of maternal vascular malperfusion, including accelerated villous maturation, villous infarction, distal villous hypoplasia, decidual arteriopathy, and/or superficial implantation. Additional placental lesions sometimes associated with decreased weight and increased FPR include high-grade chronic villitis, chronic histiocytic intervillositis, and massive perivillous fibrin deposition (maternal floor infarction). Most other

histopathologic lesions associated with an SGA placenta, such as fetal vascular malperfusion or chronic abruption, do not typically show an increased FPR. LGA placentas with a significantly decreased FPR often show delayed villous maturation. LGA placentas with a normal FPR are usually histologically normal while LGA placentas with an increased FPR may show early signs of maternal vascular malperfusion such as focally increased syncytial knots. All of these specific lesions are discussed elsewhere in this volume.

Ancillary Diagnostic Testing: A placental weight of over 1,000 g is distinctly unusual and diagnostic testing to exclude hydrops fetalis, metabolic storage disorders, fetoplacental overgrowth disorders such as BWS, or androgenetic biparental mosaicism/chimerism (also known as placental mesenchymal dysplasia; see Chapter 9) may be warranted[7,8,12–15]. Term or near term placentas weighing less than 250 g are similarly unusual and can have genetic/chromosomal abnormalities such as confined placental mosaicism. Pregnancies with this degree of placental weight reduction can be accompanied by fetal osteopenia and reduced long-bone growth that sometimes requires exclusion of skeletal dysplasia[24].

Prognostic Implications: SGA placenta and increased FPR are independent risk factors for stillbirth, while LGA placenta and decreased FPR are independent risk factors for NICU admission and adverse short-term neonatal outcome[25,26]. Increased placental weight has recently been correlated with increased weight for height in 2-year-old infants[27]. This association was is independent of maternal BMI. Much of the current interest in placental weight and FPR has been spurred by Barker's seminal paper on the fetoplacental origins of adult disease[28]. Several other studies have shown a positive correlation between increased placental weight and elevated systolic blood pressure in later life, but not during infancy[29,30]. In many of these studies, overall cardiovascular mortality was increased later in life, and the effects were most pronounced when increased placental weight was combined with decreased birth weight (i.e. decreased FPR). The underlying basis for these observations remains uncertain. A popular hypothesis is that they represent epigenetic alterations in key metabolic pathways triggered by abnormal gestational levels of growth factors, corticosteroids, and dietary fat.

Knowledge Gaps: Which histologic subgroups of LGA placentas place the fetus at greatest risk for later adult disease is unknown. Confounding effects of genetic inheritance, nutritional status, maternal obesity, and the postnatal environment have not been fully excluded.

Abnormal Length, Width, or Thickness (Chorion Regression, Elongated Placenta, Thin Placenta, Large Placental Surface Area, "Cupcake Placenta," "Jelly-Like" Placenta, Focal Placental Atrophy)

Definition: Significant variation from the expected value for GA of placenta length (maximum diameter), width (minimum diameter), difference between length and width, surface area (as estimated by ellipse formula, length x breadth x $\pi/4$), and/or thickness (either directly measured or estimated by surface area/weight). A related process, *focal placental atrophy*, can be defined as 10 percent or more of parenchyma, usually marginal, showing reduced thickness (less than half) relative to the remaining placenta (Figure 16.1)[31].

Clinical Context: The potential value of combining abnormal placental dimensions with fetal/placental weights and histologic findings for establishing clinically relevant pregnancy phenotypes is intriguing but unproven. Some relevant studies have used old clinical datasets with placental measurements performed by non-pathologists to define relationships with birth weight and/or long-term cardiovascular complications. Others have explored the ability of early sonographic measurements such as reduced chorionic length, decreased length/thickness ratio, and an increased asymmetry index (increased length minus width/length) to predict severe FGR and adverse neonatal outcomes[32]. Salafia showed a correlation of increased placental thickness with eccentric UC insertion and found that both were independently associated with decreased FPR[17]. Another report documented an association of decreased width with preeclampsia[33]. Finally, one recent study described an association of decreased placental surface area and increased length/width ratio with a clinical diagnosis of retained placenta[34].

Proposed Pathogenesis: Decreased maximum diameter (so-called chorion regression) has been hypothesized to relate to superficial implantation and a paucity

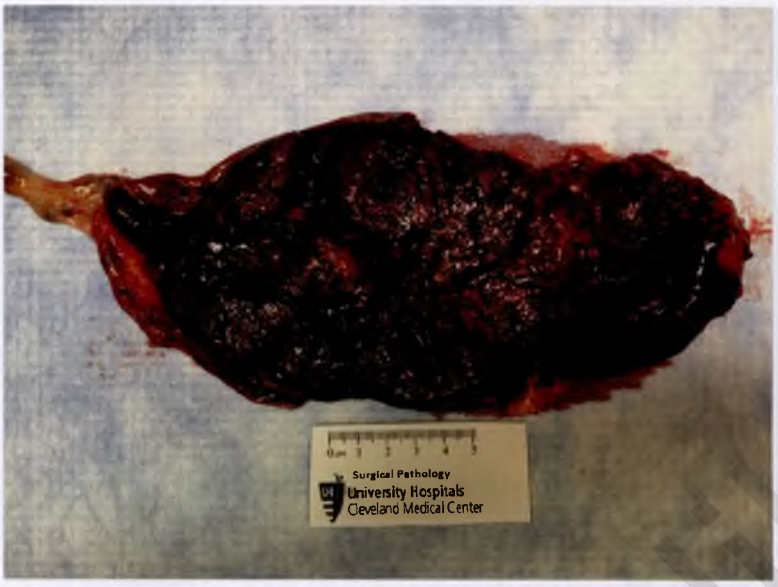

Figure 16.3 Elongated placenta. Placental length, usually representing the rostral-caudal fetal axis, significantly exceeds its width, usually representing the lateral fetal axis.

of early endovascular trophoblast plugs within marginal spiral arteries[35]. Lack of arterial plugs is believed to increase marginal oxygen tension, stimulate parenchymal to membrane conversion, and decrease the placental diameter[36]. Another theory, based on indirect evidence from epidemiologic studies, is that placental length is genetically determined, while width is a "nutritional sensor" that varies according to the mother's nutritional status during pregnancy[37]. In this scenario, it is assumed that length represents rostral-caudal growth, and width lateral growth. While possible biologic explanations can be envisioned, this hypothesis is largely speculative. Furthermore, as Salafia and colleagues have pointed out, while the measurement of maximum length is straightforward, width is more subjective, particularly in irregularly shaped placentas[38]. They argue that degree of irregular contour, rather than width, is a more reliable measurement. Finally, thin placentas with a large surface area have been shown to be more efficient (increased FPR), possibly due to an increased number of cotyledons and spiral arteries compared with short thick placentas of the same weight[39,40].

Gross Features: In general, placental length is correlated with the length of the infant[37]. Decreased length (maximum diameter <10 cm by ultrasound) is associated with severe FGR, abnormal antenatal serum markers (PAPP-A, hCG, AFP, Inhibin), lack of diastolic flow on umbilical arterial Doppler studies, and early preterm birth[32,41]. Decreased width alone and an increased difference between length and width are both more common with preeclampsia and FGR (Figure 16.3)[33]. A rounder placenta (equal length and width) has been reported in a diverse group of clinical situations including maternal malnutrition, a pro-diabetic variant of the PPAR-gamma gene, childhood obesity, and adult cardiovascular disease[42–44]. Surface area and thickness are normally proportional to placental weight. Abnormally short, thick placentas (so-called cupcake placentas) have been associated with hypertension and FGR[35,40]. A few caveats regarding thickness are (1) thickness of the delivered placenta may not accurately reflect thickness in vivo (see below), (2) estimating average thickness by dividing weight by the calculated surface area, as in Appendix 9) is compromised by nonelliptical shapes and variable tissue densities, and (3) there can be marked regional variation in thickness (e.g. focal placental atrophy).

Microscopic Features: Few studies have investigated the relationship of abnormal placental dimensions to histologic findings. Placentas with a short chorionic diameter and increased thickness in vivo often show distal villous hypoplasia (see Chapter 6)[45]. Interestingly, the increased thickness observed by ultrasound was often not detectable following delivery. This discrepancy was attributed to a paucity of anchoring villi resulting in overexpansion of the intervillous space in vivo with "deflation" at delivery[46]. This lack of basal plate support might also

explain the wobbly, "jelly-like" appearance of these placentas seen on antenatal ultrasounds[41,47]. Finally, most experienced placental pathologists would agree that accelerated villous maturation and focal placental atrophy often accompany placentas with increased length minus width and irregular contour.

Ancillary Diagnostic Testing: Increasingly sophisticated antenatal imaging techniques can predict abnormal placental dimensions in some cases.

Prognostic Implications: Aspects of the extreme phenotypes, (a) decreased maximum diameter, increased length minus width, and increased thickness and (b) increased width, increased chorionic plate surface area, and decreased thickness, may identify different subsets of SGA fetuses with respect to later risks for obesity, abnormal glucose tolerance, and adult cardiovascular disease.

Knowledge Gaps: While qualitative relationships between placental dimensions and long-term cardiovascular complications have been demonstrated; the causal pathway is unclear. Whether these measurements add value beyond histopathology and fetal or placental weights remains to be established.

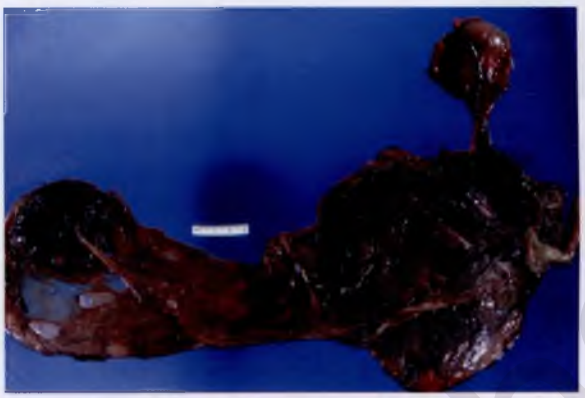

Figure 16.4 Multiple accessory lobes. Several smaller lobes are separated from the main placental disc (lower right) by membranes and bridging fetal blood vessels.

PLACENTAL SHAPE

Abnormal Contour (Accessory Lobe, "Succenturiate" Lobe, Bilobed Placenta, Multilobed Placenta, Irregular Placental Contour, Type 2 Vasa Previa)

Definition: Significant variations from the normal smooth contour of the placental disc including the following: *accessory (also known as "succenturiate") lobe* – a distinct island of parenchyma separated from the disk by 2 cm or more (Figure 16.4), *bilobed or multilobed placenta* – parenchymal indentation(s) of 50 percent or greater (Figure 16.5), and *irregular*

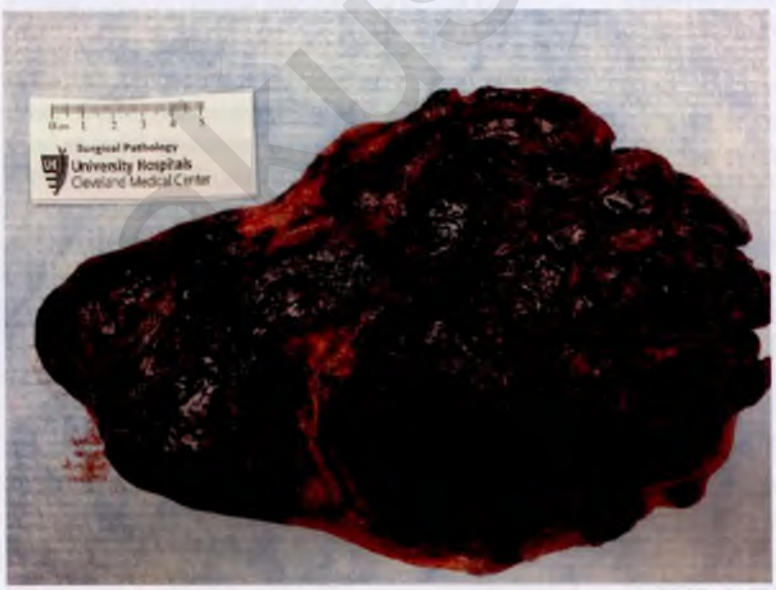

Figure 16.5 Multilobed placenta. A narrow bridge of placental tissue lies between small (<50 percent, top) and deep (>50 percent, bottom) indentations into the placental disc.

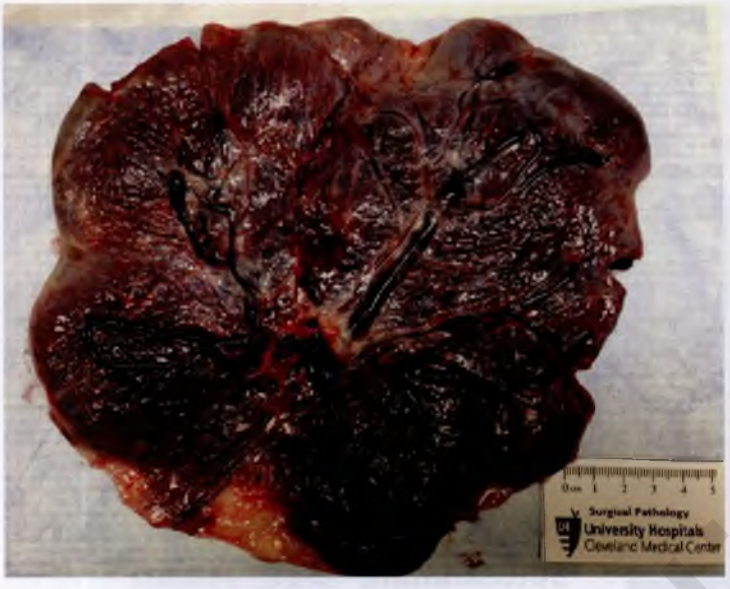

Figure 16.6 Irregular placental contour. Undulating peripheral outline with small indentations (<50 percent).

placental contour – lesser indentations defined qualitatively by inspection or quantitatively by metrics such as the "star diameter" (Figure 16.6)[6,31].

Clinical Context: Accessory lobes are seen in 3–8 percent of all placentas[48,49]. There are no reliable incidence figures for other variations in contour. The most pressing clinical issue in these cases is to identify large fetal vessels that bridge the gaps between placenta and accessory lobes or indentations, particularly if these vessels overlie the cervix (type 2 vasa previa)[50]. Accessory lobes can also become detached from the placenta during parturition, leading to retained placental fragments that can develop into placental polyps. Irregular placental contour may sometimes reflect growth around underlying uterine lesions such as leiomyomas or scars, lesions that may predispose to placenta previa or accreta in subsequent pregnancies (see Chapters 27 and 28).

Proposed Pathogenesis: There are 3 major theories explaining abnormal placental contour. The first posits that the fetal pole of the blastocyst may be eccentric at the time of implantation, resulting in asymmetric placental development[51]. The second, "trophotropism," suggests that placentas become irregular by preferentially occupying richly vascularized uterine tissue and avoiding less well-vascularized areas, such as the lower uterine segment, uterine scars, or leiomyomas[52]. The third postulates that defective growth and branching of large chorionic plate vessels in the late first trimester create parenchymal deficiencies in "watershed areas" that cannot be completely "filled in" by later villous development[6]. Evidence supporting the last theory is based on mathematical modeling and detailed analysis of placentas from historical birth cohorts, prospective studies using early ultrasound, in vitro fertilization pregnancies, and familial autism/autism spectrum disorder registries. These theories are mutually exclusive.

Gross Features: In general, placentas with abnormal contour are slightly decreased in weight, vary in thickness with firm yellow areas of focal atrophy, often at the margins, and can have unprotected large fetal vessels traveling in the membranes to accessory lobes or bridging areas of indentation. These should be carefully inspected for tears showing adjacent hemorrhage and correlated with fetal outcome and hematocrit. Likewise, the maternal surface should be examined looking for areas of disruption which may indicate retained villous tissue and/or placenta accreta.

Microscopic Features: Unless they show gross abnormalities, it is not necessary to submit sections from accessory lobes. While the boundary between membranes and placental parenchyma in abnormally shaped placentas is sometimes sharply demarcated, there is often a gradual transition with areas of parenchymal thinning and placental atrophy.

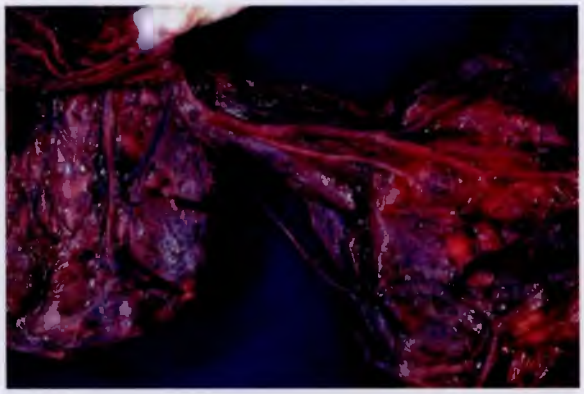

Figure 16.7 True bilobate placenta. Two approximately equal placental discs are bridged by fetal vessels arising from an umbilical inserted in the intervening membranes near the smaller disc.

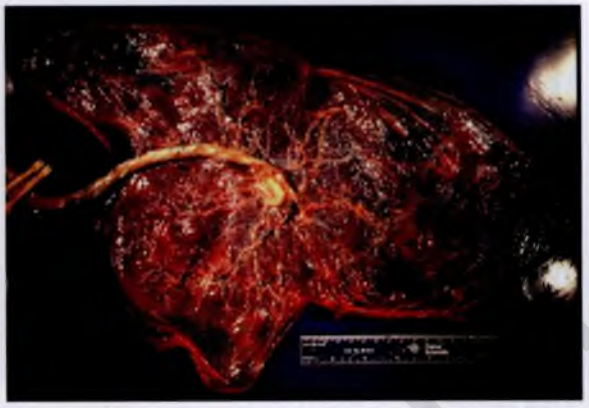

Figure 16.8 Placenta membranacea. A uniformly thin placenta with a very large fetal surface area shows only focal areas of true membrane formation.

Histologically, these atrophic areas show simplification of villous branching and large amounts of bland intervillous and perivillous fibrin(oid) resembling perivillous fibrin plaques (see Chapter 17). Some evidence suggests that abnormal contour and histologic lesions are independent predictors of placental function[17].

Ancillary Diagnostic Testing: Abnormal placental contour can be detected by ultrasound in the late first or early second trimester[53]. Sophisticated methods for quantitating the magnitude and exact nature of irregular contour in the delivered placenta such as calculating star diameters, the standard deviation of multiple placental radii, or the fractal coefficient of chorionic vessel branching are research techniques without specific clinical applications at this time[54].

Prognostic Implications: Birth weight is often mildly reduced and fetoplacental weight ratio slightly elevated in placentas with an abnormal contour[17]. The long-term consequences of these small differences are unknown. Major fetal hemorrhages due to laceration of intramembranous vessels during parturition (ruptured vasa previa) can lead to death or major CNS injury. Since underlying uterine anatomy and inherited genetic abnormalities involving fetal vascular patterning could both affect placental morphogenesis, these lesions have the potential to recur in subsequent pregnancies.

Knowledge Gaps: The biologic determinants of abnormal placental contour remain controversial. To what extent irregular contour is a risk factor alone or in combination with other placental lesions for adverse outcomes is unclear.

Rare Developmental Anomalies: True Bilobate Placenta and Placenta Membranacea

Definition: A true *bilobate* (also known as *bipartite*) *placenta* has 2 more or less equal-sized lobes separated by membranes, which usually contain the umbilical cord insertion site (Figure 16.7). *Placenta membranacea* is a chorionic sac completely or near completely surrounded by a thin layer of villous parenchyma without a significant membranous component (Figure 16.8).

Clinical Context: The incidence of true bilobate placenta has been estimated at 0.3–0.9 percent[49,52]. Placenta membranacea is an extremely rare condition with fewer than 50 reported cases in the literature[55]. More than half of these reported cases contain at least some membranous component (partial placenta membranacea). Estimates of incidence for placenta membranacea range from 1/3500 to 1/25,500. Based on the author's experience, the latter seems more credible. True bilobate placentas and placenta membranacea both have a high associated incidence of associated placenta previa and vasa previa and are at significant risk for fetal hemorrhage due to rupture of parenchyma or large fetal vessels during labor and delivery. Both conditions are also associated with recurrent vaginal bleeding at all stages of pregnancy and have an increased risk of placenta accreta[56,57].

Proposed Pathogenesis: The pathogenesis of these rare developmental abnormalities is unclear. Interestingly, they at least in part, recapitulate features of other primate placentas – bilobate, seen in rhesus

monkeys, and diffuse (membranacea), seen in some lower primates. They could represent either rare genetic conditions or extreme ends of the normal developmental spectrum (i.e. bilobate placenta transitioning from a large accessory lobe and placenta membranacea from a thin placenta with increased surface area). An older theory of bilobate placenta is that very early shallow implantation might lead to significant parenchymal development on both sides of the endometrial cavity. More recently, bilobate placentation has been modeled by proposing an elongated axis of fetal chorionic vasculogenesis, stunted along its mid portion but more active at both ends[6]. The transformation of the placenta from a homogeneous chorionic sac to distinct villous parenchyma (chorion frondosum) and thinned chorionic membranes (chorion laevae) begins at about 8–10 weeks gestation. As described in the previous section, increased early marginal blood flow may cause an increase in the membranous component in chorion regression syndrome. By analogy, a global reduction in early blood flow could lead to an increase in the parenchymal component and deficient membranes in placenta membranacea. Along these lines, some evidence suggests that placenta membranacea is associated with endometrial abnormalities including chronic inflammation, mechanical injury, abnormal vascularization, and hypoplasia[55].

Gross Features: The distinction between bilobate placenta and a large accessory lobe with membranous insertion of the umbilical cord in the intervening membanes is somewhat arbitrary. Villous tissue must occupy at least 2/3 of the expected membranous area to make a diagnosis of placenta membranacea. Additional gross features supporting a diagnosis of placenta membranacea are a markedly enlarged surface area and uniformly decreased placental thickness. Areas of old and recent retroplacental blood clot and disruption of the basal plate often accompany placenta membranacea.

Microscopic Features: There are no consistent histologic findings associated with either of these rare lesions. Histologic evidence of old or recent retroplacental hemorrhage (membrane hemosiderin, overlying villous infarcts), focal placental atrophy, and/or foci of placenta accreta (basal anchoring villi directly implanting on smooth muscle) may be seen in both conditions.

Ancillary Diagnostic Testing: None.

Prognostic Implications: Both lesions are associated with catastrophic fetal hemorrhages and placenta accreta. Recurrence risk is unknown.

Knowledge Gaps: It is not known if these unusual developmental anomalies are genetically determined variants recapitulating placental types seen in lower primates or extremes in the spectrum of human placental development.

UMBILICAL CORD ABNORMALITIES

Abnormal Insertion Site (Membranous / Velamentous, Marginal, Peripheral, Furcate, Furcate with Interposition, Amnion Web / Tethered, Aberrant Membranous Vessel / Ectopic Chorionic Vessel in Membranes, Type 1 or 3 Vasa Previa)

Definition: Variations as follows from the normal state of a freely movable, paracentrally inserted umbilical cord (UC) completely surrounded by Wharton's jelly:

membranous/velamentous insertion – UC inserted in the placental membranes (Figure 16.9),

marginal insertion – UC inserted in the placental disc 0.5 cm or less from the margin,

peripheral insertion – UC inserted in the placental disc less than 3 cm from the margin (Figure 16.10),

furcate insertion – UC inserted in the placental disc with distal vessels unprotected by Wharton's jelly at the insertion site (Figure 16.11),

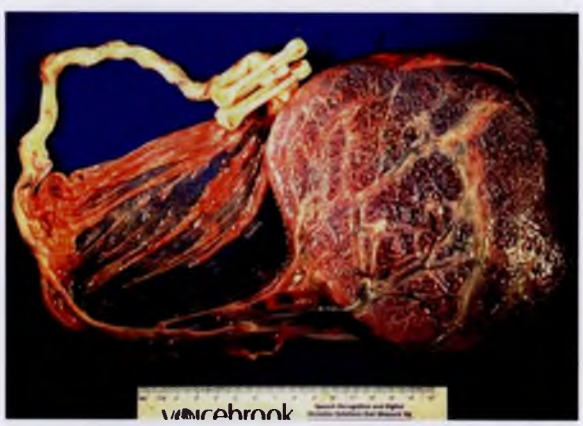

Figure 16.9 Membranous insertion of umbilical cord.

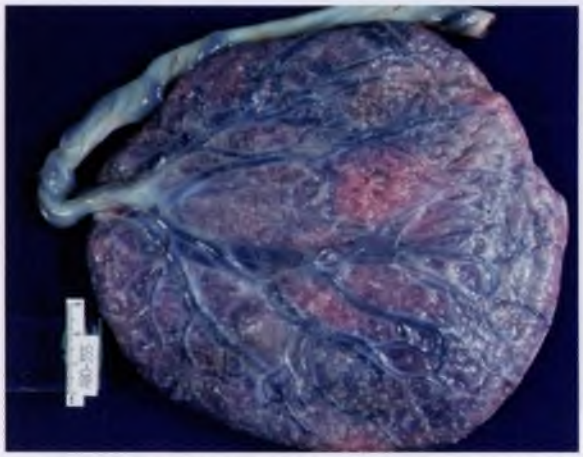

Figure 16.10 Peripheral insertion of umbilical cord.

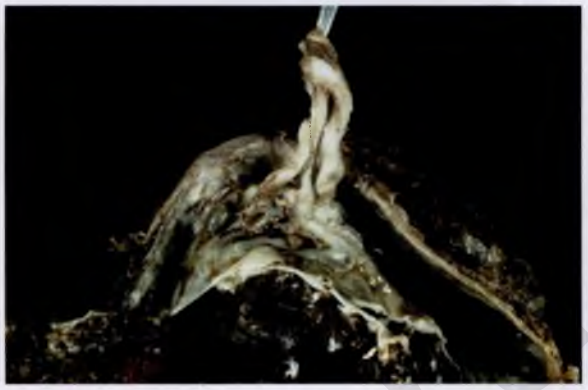

Figure 16.11 Furcate insertion of umbilical cord. Umbilical cord inserts peripherally into the placental disc. Chorionic vessels are exposed without surrounding Wharton's jelly proximal to the placental insertion site.

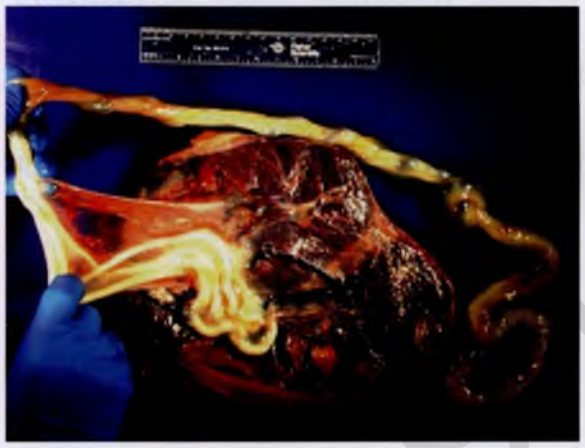

Figure 16.12 Furcate insertion with interposition of umbilical cord within a fold of amnion. Exposed chorionic vessels are further placed at risk for torsion by the restrictive fold of amnion.

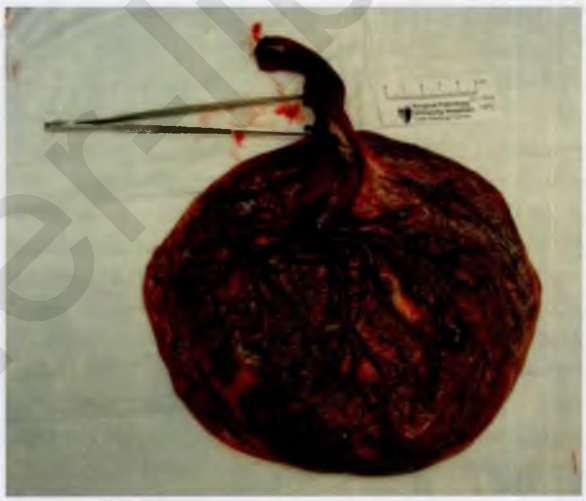

Figure 16.13 Nonmembranous umbilical cord with tethering amnion web. Umbilical cord is normally inserted but surrounded by a tight web of tethering amnion restricting its free movement in all directions.

furcate insertion with interposition – furcate vessels coursing through a large fold of amnion prior to insertion into the placental disc (Figure 16.12),

amnion web/tethered UC – insertion into the placental disc, but with mobility restricted by a "tethering" fold of amnion (Figure 16.13), and

aberrant membranous vessel – insertion into the placental disc, but with a chorionic vessel partially traversing the membranes (Figure 16.14).

Vasa previa is a clinical diagnosis defined by unprotected fetal vessels overlying the cervical os. There are three subtypes: type 1 – associated with membranous UC insertion, type 2 – associated with abnormal placental contour (see above), and type 3 – associated with an aberrant membranous vessel[50].

Clinical Context: Membranous (also known as velamentous) UC insertion is seen in 1–1.5 percent of placentas, marginal insertion in 7–10 percent, and peripheral insertion in 9–11 percent[48,58]. All 3 types of non-paracentral UC insertion are more common in placentas from spontaneous preterm births and could reflect developmental abnormalities contributing to causation in some cases. Sonographic studies indicate that non-paracentral UC insertion can be diagnosed by as early as 14 weeks of

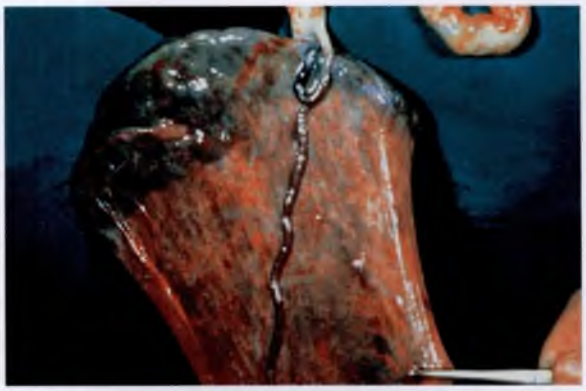

Figure 16.14 Nonmembranous umbilical cord with an aberrant membranous vessel.

gestation[53]. Underlying maternal risk factors include obesity, primiparity, smoking, and infertility[59]. Fetoplacental risk factors include preeclampsia, FGR with abnormal umbilical pulsed flow Doppler studies, and elevated first trimester maternal serum hCG and AFP[35,60–62]. Prevalence is increased in multiple gestations where non-paracentral UC insertions are significantly associated with discordant fetal growth in both dichorionic and monochorionic twin gestations[63]. Membranous UC insertion, in particular, is associated with an increased risk of stillbirth in monochorionic twins and preterm delivery for all twins[64]. Membranous UC insertion in singleton pregnancies has been associated with congenital anomalies, particularly deformations[65]. Antenatal diagnosis and early elective delivery are the cornerstones of management for all types of vasa previa.

Proposed Pathogenesis: Theories explaining non-paracentral UC insertion overlap with those for abnormal contour (see above)[17]. Both conditions appear to be largely determined early in pregnancy. UC insertion is generally believed to be central at the time of implantation. Major chorionic vessels normally elongate and branch in a symmetric fashion to form the slightly ovoid placenta with paracentral UC insertion site usually seen at delivery[6]. Nonuniform development of placental parenchyma relative to the UC insertion site may be caused by "trophotropism" or asymmetries along the fetal vasculogenic axis, as discussed in the previous section. The overall branching pattern of major chorionic plate vessels ranges from the so-called disperse/dichotomous branching pattern, usually seen with paracentral UC, to the magistral/monopodal (perpendicular branching off a major trunk) pattern, usually seen with non-paracentral UC. Mathematical modeling suggests that each pattern maximizes perfusion for its respective UC insertion type[66]. The pathogenesis of furcate and tethered UC insertions is unclear.

Gross Features: In addition to increased frequency in twins, non-paracentral UC insertion is associated with decreased placental weight, increased thickness, irregular shape, and abnormal location (e.g. placenta previa)[67,68]. Non-paracentral UC are also often thin (<8 mm in cross-sectional diameter)[69]. An association with decreased FPR has also been reported[17].

Microscopic Features: Non-paracentral UC insertion, especially near term, is more frequent in placentas with features of maternal vascular malperfusion. Membranous, furcate, and tethered UC insertion sites are at high risk for intermittent fetal vascular obstruction (global/partial fetal vascular malperfusion; see Chapter 10). Accompanying histologic features of the latter may include vascular ectasia and intramural fibrin deposition in large chorionic and stem villous veins and small foci of avascular villi. In some cases, chronic fetal circulatory stasis can progress to thrombosis with large foci of avascular villi (segmental/complete fetal vascular malperfusion)[70].

Ancillary Diagnostic Testing: Recent studies indicate that the site of umbilical cord insertion can be predicted by late first trimester ultrasound[6].

Prognostic Implications: Unprotected fetal vessels travelling within the membranes can be torn during delivery leading to significant fetal hemorrhage into adjacent tissues (e.g. ruptured vasa previa)[71]. Ruptured vasa previa can lead to CNS damage or stillbirth. Vasa previa has recently been associated with a high prevalence of associated fetal malformations, especially cardiovascular[50]. Recurrence risk for non-paracentral UC insertion is unknown.

Knowledge Gaps: The relative contribution of primary malformation versus secondary deformation in the genesis of non-paracentral UC insertion remains controversial. Whether abnormal insertion is an independent risk factor for spontaneous preterm birth or FGR is unproven. An underlying genetic component has not been excluded.

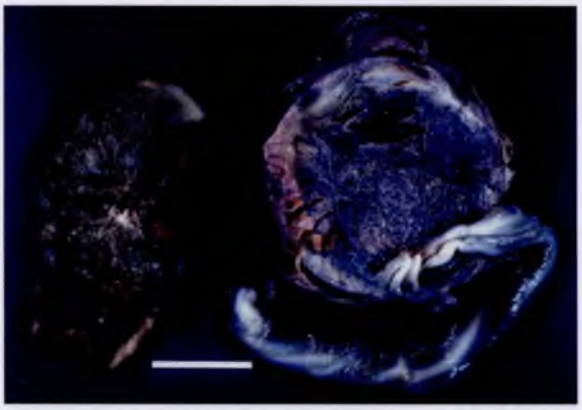

Figure 16.15 Thick umbilical cord. Diffusely enlarged umbilical cord (lower right) exceeds 2 cm in maximum diameter (note: same case illustrated in Figure 16.2).

Abnormal Length and/or Thickness (Long UC, Short UC, Thin UC, Decreased Wharton's Jelly, Thick UC, Increased Wharton's Jelly, UC Edema)

Definition: An excessively *long UC* is commonly defined as greater than 70 cm with greater than 95 cm considered *extremely long*[72]. *Short UC* should only be diagnosed if submission of the entire UC can be confirmed, something rarely known with certainty. A *thin UC* (diffusely decreased Wharton's jelly) has been defined as less than 0.8 cm in maximum thickness as measured on a slide containing two or more representative sections[21]. A *thick umbilical cord* (diffusely increased Wharton's jelly) has been defined by one author as more than 2 cm average diameter (Figure 16.15)[48].

Clinical Context: Long UC are prone to cord entanglements (e.g. nuchal or body cords, true knots, cord prolapse) that may result in acute and/or chronic reductions in fetoplacental blood flow[73]. Additional consequences and complications of long UC include increased resistance owing to length alone (1.5-fold increase in length leads to a 33 percent decrease in flow by Pouiselle's law) and excessive coiling (see next section); both of which can also compromise fetal placental perfusion. Other reported associations include reduced Apgar scores, birth asphyxia, nonreassuring fetal monitoring, neonatal respiratory problems, and neurodisability. Short UC generally reflects decreased fetal movement and associated clinical conditions can be separated into intrinsic or extrinsic categories[74]. The intrinsic group includes CNS and muscular anomalies, severe limb deficiencies, and urinary tract malformations associated with severe oligohydramnios. The extrinsic group includes other causes of severe oligohydramnios, a restrictive endometrial environment (e.g. uterine malformations or large leiomyomas), and amnion bands that tether the fetus to the placenta. The most extreme example of the latter is *early amnion rupture sequence* characterized by short UC, ventral wall anomalies and facial/ CNS disruptions (see Chapter 21). Short UC has been associated with a "cord compression" pattern on fetal monitoring, but is no longer believed to be a significant cause of dystocia relating to an arrest of descent[75]. Thin UC/ decreased Wharton's jelly is associated with FGR, early onset preeclampsia, poor 5-minute Apgar, and NICU admission[69,76–78]. Thick UC can be seen with maternal diabetes, fetal Beckwith-Wiedemann syndrome, and hydrops fetalis[79].

Proposed Pathogenesis: Animal models suggest that the length of the UC in late pregnancy is primarily determined by fetal movement[80] Long UC is thought to reflect increased fetal movement leading to stretch-related lengthening and remodeling. UC entanglements may augment stretching and are another associated factor. Conditions limiting or restricting fetal movement, as described above, prevent stretching resulting in a short UC. Developmental anomalies associated with UC length of less than 10 cm have been classified into 6 groups, details of which are beyond the scope of this discussion[48]. Interestingly, birth-weight percentile declines on both sides of the mean for UC length for GA[81]. Thin UC usually reflects decreased hydration of the Wharton's jelly, often as part of a generalized decrease in extracellular fluid with uteroplacental insufficiency. Increased extracellular fluid due to fetal congestive heart failure (hydrops fetalis) can lead to a thick UC. Variations in the synthesis of Wharton's jelly mucopolysaccharides in diabetes and maternal vascular malperfusion also contribute to UC diameter[82].

Gross Features: Standardized tables with percentiles for gestational age are available for both UC length (see Appendix 6) and diameter[69,83]. Of note, formalin fixation has been shown to shorten UC length by approximately 12 percent[84]. Long UC are prone to

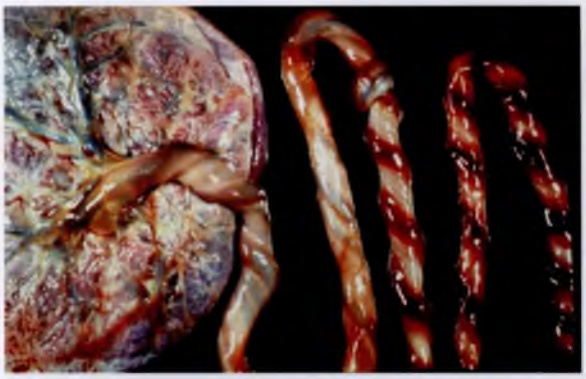

Figure 16.16 Long umbilical cord with "tight" true knot. Note the clear distinction between umbilical cord morphology proximal and distal to the knot.

Figure 16.17 Long, hypercoiled umbilical cord, stillborn. Increased coiling index with right twist plus indentations and vascular dilatation.

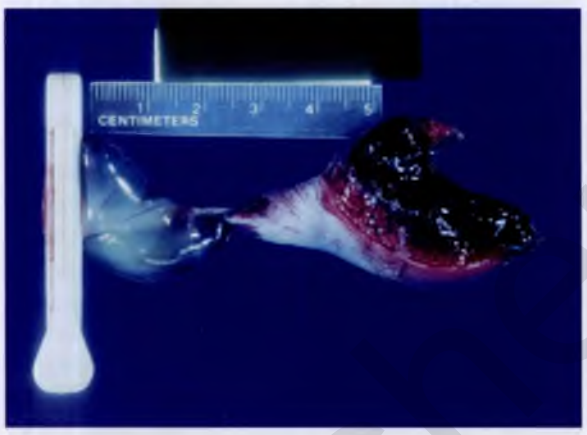

Figure 16.18 Umbilical cord stricture, stillborn. Recent stillbirth with true stricture separating the edematous umbilical cord (left) from the fetal umbilicus and adjacent body wall (right).

entanglements and hence are often associated with meconium staining (see Chapter 19). Long UC should be further inspected for obstructive lesions (knots, hypercoiling, strictures) (Figures 16.16–16.18). Placentas associated with short UC should be carefully scrutinized for signs of oligohydramnios (amnion nodosum) or amnionic bands (see Chapter 21). Typical features accompanying thin UC include decreased fetal and placental weights, increased fetoplacental weight ratio, and villous infarcts. Thin UC are also more common with single umbilical artery, marginal or membranous UC insertion, and in placentas from the smaller of discordant twins. Placentas with thick UC are usually large and, when associated with hydrops fetalis, may show pale edematous parenchyma.

Microscopic Features: Long UC, particularly when complicated by hypercoiling or entanglements, is associated with histologic features of global partial/intermittent fetal vascular malperfusion (see Chapter 10). These include scattered small foci of avascular villi, ectasia or intramural fibrin deposition affecting chorionic and proximal villous veins, and patchy delayed villous maturation or edema. There are no consistent histologic features accompanying short UC. Thin UC is often accompanied by histologic features of maternal vascular malperfusion (see Chapter 7). Delayed villous maturation (diabetes), villous capillary lesions, and dysmorphic villi (see Chapter 9) may accompany a thick UC.

Ancillary Diagnostic Testing: None.

Prognostic Implications: Long UC can lead to IUFD due to complete UC obstruction following entanglement, prolapse, or a tight true knot. Global partial/intermittent vascular fetal malperfusion secondary to long UC has been associated with neurodisability[70,85]. Short UC should prompt consideration of underlying CNS/neuromuscular disease (fetal akinesia sequence) or a restrictive intrauterine environment (oligohydramnios/ deformation sequence). Thin UC are easily compressed and therefore more susceptible to UC accidents.

Knowledge Gaps: Better antenatal diagnostic modalities to prospectively evaluate the UC are needed.

Coiling/Strictures (Hypercoiled UC, Hypertwisting, Excessive Coiling, Hypocoiled UC, Decreased Coiling, Abnormal Coiling Index, Left-Twisted UC, Right-Twisted UC, UC Stricture)

Definition: A *hypercoiled UC* has more than 3 diagonal grooves in a 10 cm segment (>0.3/cm). Risk of obstructed blood flow increases with the numbers of coils and the degree of indentation between coils (Figure 16.17)[86]. A *hypocoiled UC* has one or fewer coils/10 cm. Directionality of coiling may be important (see below): a *left-twisted UC* has diagonal grooves extending from the upper left to the lower right of the UC segment and a *right-twisted UC* the opposite. *UC strictures* are regions of narrowing (less than 1.3 mm diameter in one study), sometimes multiple, most frequently observed in stillbirths near the UC insertion site into the body wall (Figure 16.18)[87].

Clinical context: Hypercoiled UC has been associated with stillbirth, fetal heart rate abnormalities, birth asphyxia, low 5-minute Apgar scores, and FGR, particularly after 36 weeks[88,89]. The percentage of hypercoiled UC showing a left twist is less than that seen with normal coiling, and hypercoiled UC with a right twist are at higher risk for an adverse outcome[90]. Recent data also suggest that adverse outcomes are primarily seen in hypercoiled UC with indentations between coils[86]. Also, factors such as decreased UC thickness, increased length, and eccentric placental insertion site can interact with hypercoiling to further compromise umbilical blood flow.

Hypocoiled UC has been associated with IUFD, fetal monitoring abnormalities, reduced umbilical venous flow by Doppler, multiple pregnancy, preterm delivery, aneuploidy, and single umbilical artery[91–93]. Similar to hypercoiled UC, the percentage of hypocoiled UC showing a right twist exceeds that seen with normal coiling[91]. Interestingly, in monochorionic twins with twin transfusion syndrome, the donor more commonly shows hypocoiling while the recipient more commonly shows hypercoiling[94].

UC strictures are associated with stillbirth and multiple gestation[87,95]. Surprisingly, some authors have reported recurrence of strictures in subsequent pregnancies[95,96]. Twin studies suggest that recurrence does not have an underlying genetic basis, but such studies may be underpowered to show a small effect[97].

Proposed Pathogenesis: The majority of UC (95 percent) demonstrate an inherent irreducible twist fixed by spiraling of the arteries around the vein. This twist appears to be determined early in pregnancy, and coiling indices measured in utero generally agree closely with those determined after birth[90]. For reasons that are not clear, left twisting is more common than right twisting by a 7:1 ratio[91]. The underlying basis for coiling and its directionality is not understood, but could potentially relate to either the normal clockwise rotation of the gut as it returns to the abdomen early in pregnancy or contraction of the Roach muscle, which is asymmetrically attached to the umbilical arteries at the placental insertion site[98]. Another possibly contributing factor is the generally increased diameter of the right compared with the left umbilical artery. Proposed adaptive advantages of coiling include (1) allowing the UC to be stretched like a phone cord, (2) utilizing the spiraling umbilical arteries to surround and protect the umbilical vein, and (3) employing arterial pulsations as a countercurrent peristaltic pump to help move oxygenated umbilical venous blood toward the fetus[99]. UC strictures can be seen alone or in combination with hypercoiling[87]. In the latter case, they may develop by gradual accentuation of the indentations between coils. Experimental studies in animals have also shown that transient compression of the UC in early pregnancy can lead to a later stricture[48]. The most common site of stricture is near the fetal insertion site, a finding that may be explained by physiologic constriction of the umbilical ring near the fetal umbilicus in the second half of gestation[100].

Gross Features: Hypercoiled UC have been separated into 4 groups based on the degree of indentation between coils: undulating, rope-like (both nonindented), segmented (less than 50 percent indentation), and linked (greater than 50 percent indentation)[90]. Only the last 2 are associated with adverse outcomes. Magnitude of coiling appears to be similar in the mid and placental ends of the UC but increased near the fetal body-wall insertion site, a feature which could help explain the increased frequency of strictures at this location[101]. Hypercoiling is more common with an eccentric placental insertion site and hypocoiling with a single umbilical artery[88,91].

Microscopic Features: As for other potentially restrictive UC abnormalities (see previous two sections), hypercoiled UC can be associated with

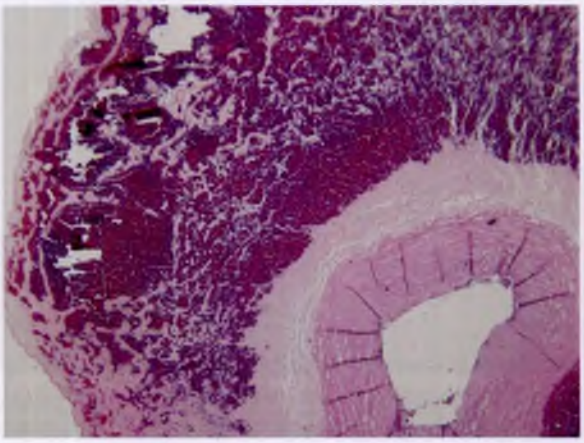

Figure 16.19 Intrafunicular hemorrhage, umbilical cord. Fresh hemorrhage dissects though Wharton's jelly without any signs of organization.

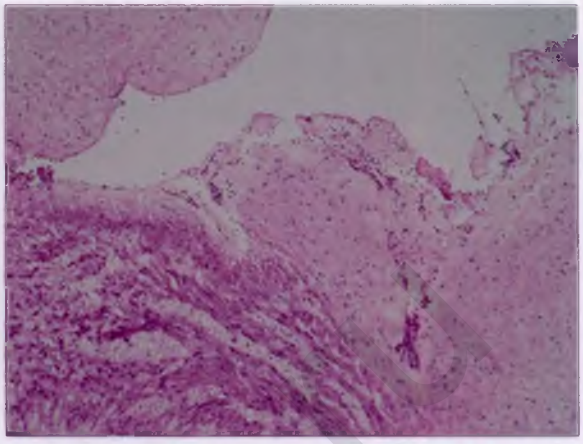

Figure 16.20 Umbilical cord surface ulcerations. The wall of the umbilical vein (lower left) is in direct contact with the nonepithelialized exterior surface of the umbilical cord. Wharton's jelly contains numerous vacuolated, pigment-laden macrophages.

histologic features of fetal vascular malperfusion (see Chapter 10)[90]. Most commonly, this is global/ partial with small foci of avascular villi, proximal venous dilatation and/or intramural fibrin deposition, and delayed villous maturation[102]. Occasionally, stasis can progress to thrombosis of umbilical, chorionic, or stem villous vessels (segmental/ complete fetal vascular malperfusion)[70]. There are no reported histologic features associated with hypocoiled UC. Histologic examination of UC strictures may reveal thrombosis, fibrosis, and hemosiderin deposits; findings that can bolster the argument that they are not simply artefacts of maceration occurring after fetal demise[87].

Ancillary Diagnostic Testing: Not applicable.

Prognostic Implications: Hypercoiled UC is associated with stillbirth and neurodisability[90,103]. Hypocoiling is increased in stillborns, sometimes in the context of aneuploidy or other developmental abnormalities[91]. Strictures are seen in a subset of stillbirths, usually near mid-trimester, and some evidence suggests that they can recur in subsequent pregnancies (see above).

Knowledge Gaps: The mechanisms underlying UC twisting, its direction, and magnitude are unknown. Adaptive advantages of normal coiling are speculative. The optimum method to quantitate degree of coiling before or after delivery is not agreed upon. UC strictures are even less well understood, and some consider them to be secondary alterations rather than causes of death in stillbirths.

Lesions associated with loss of Integrity (UC Avulsion, Intrafunicular Hemorrhage, Cord Hematoma, Ruptured Umbilical Artery Aneurysm, Ruptured Umbilical Venous Varicosity, Surface Epithelial Ulceration, Segmental Thinning of Umbilical Vascular Smooth Muscle, Exteriorization of Umbilical Vessels)

Definition: *Avulsion of the UC* is defined as a partial or complete separation from the placenta, most commonly at the placental insertion site. *Intrafunicular hemorrhage* (cord hematoma) reflects tearing of major umbilical vessels (Figure 16.19). *Umbilical arterial aneurysms* and *umbilical venous varicosities (false knots)* are fusiform vascular lesions with attenuation of smooth muscle[104]. *Surface epithelial ulcerations* reflect either pressure or prolonged exposure to fetal gastric acid or meconium (Figure 16.20)[105,106]. Such toxic exposures can also cause *segmental thinning of umbilical vascular smooth muscle*[107] and *exteriorization of umbilical vessels* (Figure 16.21)[108].

Clinical Context and Proposed Pathogenesis: Both avulsion of the UC and intrafunicular hemorrhage are, in most cases, clinically insignificant iatrogenic lesions caused by excessive traction on the UC after delivery of

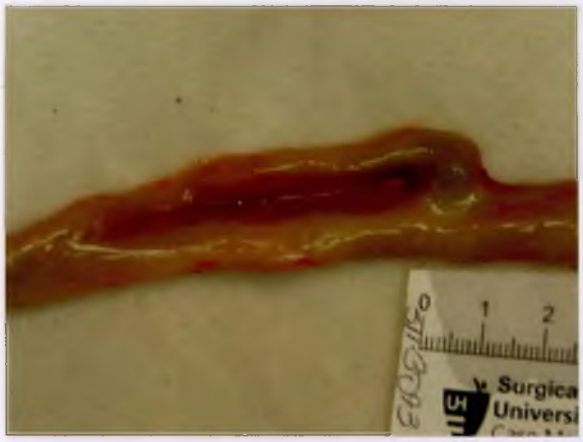

Figure 16.21 Loss of Wharton's jelly with exposed umbilical cord vessel. Faintly green-stained umbilical cord shows exteriorization of a major umbilical vessel.

the infant[48,109]. Occurrence prior to delivery of the infant is extremely rare, and diagnosis requires correlation with Apgar scores and neonatal hematocrit.

Complete or partial avulsion of the UC is associated with abnormal UC insertion sites, either fetal (e.g. omphalocele or gastroschisis) or placental (e.g. marginal/ membranous, furcate). Short or entangled UC are also at increased risk, particularly with precipitous delivery.

Iatrogenic intrafunicular hemorrhage is a rare complication of antenatal procedures such as amniocentesis, percutaneous umbilical blood sampling, or the introduction of forceps or intrauterine pressure catheters. Clinically significant sporadic intrafunicular hemorrhage usually involves an abnormal UC vessel and occurs in 1/5500 deliveries[48,110]. Venous hemorrhages are more common than arterial and typically occur in areas of varicosity, which are observed in 1–2 percent of term placentas. Arterial hemorrhages usually represent a ruptured aneurysm. Such aneurysms are increased with chromosomal abnormalities, particularly trisomy 18, and may develop following thrombosis and medial degeneration. Dissecting arterial aneurysms have been described as a cause of stillbirth[104].

Diffuse curvilinear UC surface epithelial ulcerations following the course of the umbilical vessels are associated with fetal small intestinal atresia and reflux of gastric acid into the amniotic fluid[105,106]. Prolonged meconium exposure can also cause surface ulceration, usually with a more patchy, irregular pattern[108]. Tight umbilical cord fetal entanglements are another cause of surface ulceration[111]. Segmental thinning of umbilical vascular smooth muscle and exteriorization of individual umbilical vessels may occur alone or with ulceration. All of these conditions are risk factors for catastrophic intraamniotic hemorrhage.

Gross and Microscopic Features: Avulsion can complicate long UC, thin UC, UC strictures, or membranous or furcate insertion[109]. Histologic features developing after prolonged exposure to meconium include individual myocyte necrosis, patchy loss of vascular smooth muscle cells, and, in extreme cases, loss of the muscularis or exteriorization of UC vessels (also see Chapter 19)[107,112].

Ancillary Diagnostic Testing: Not applicable.

Prognostic Implications: UC avulsion or intrafunicular hemorrhage occurring before birth are sentinel events leading to stillbirth, neonatal death, or neurodisability. Meconium associated myonecrosis can lead to fetal vascular malperfusion and an increased risk of CNS injury[103]. Presence of helical ulcerations on the UC surface should prompt a neonatal workup for small intestinal obstruction[105,106].

Knowledge Gaps: Improved methods for the antenatal detection of these abnormalities are needed.

Single Umbilical Artery and Other Anomalies of Major Umbilical Vessels (Type 1 Single Umbilical Artery, Hypoplastic/Atretic Umbilical Artery, "Fused" Umbilical Arteries Near Placental Insertion [Proximal Hyrtl Anastomosis], Type 2 Single [vitelline] Umbilical Artery, Persistent Right Umbilical Vein)

Definition: The most common major umbilical vessel anomaly is *single umbilical artery (SUA), type 1*, characterized by one or more complete sections of the UC obtained away from the placental insertion site containing only one umbilical artery which arises from either the right or left fetal internal iliac artery[48]. Other umbilical arterial abnormalities include *hypoplastic/atretic umbilical artery* (Figure 16.22) and *type 2 SUA*, where the single artery is derived from the

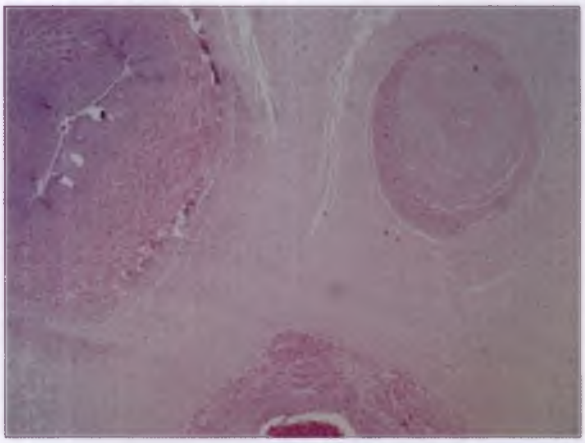

Figure 16.22 Hypoplastic second umbilical artery. One umbilical artery (upper right) shows medial necrosis and luminal obliteration. Compare to normal artery at bottom center.

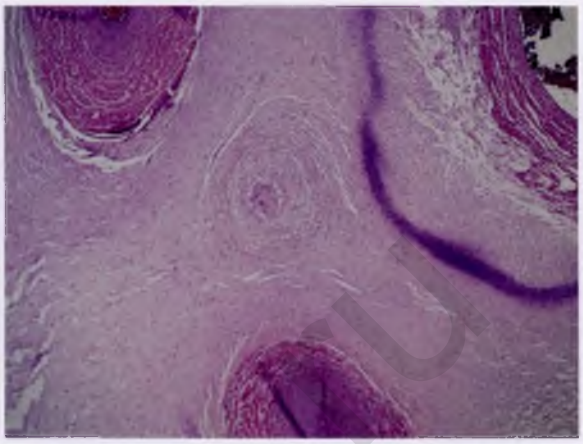

Figure 16.23 Persistent right umbilical vein. A large, muscularized vessel showing involutional changes is located between the normal (left) umbilical vein and the right and left umbilical arteries.

vitelline circulation, usually at or below the superior mesenteric artery. In UC with 4 major vessels, the extra vessel usually represents a *persistent right umbilical vein* (Figure 16.23). Considerably rarer types of *SUA (types 3 and 4)* and internal embryonic umbilical-vitelline vascular anomalies are beyond the scope of this discussion[48].

Clinical Context: Single umbilical artery (SUA) is noted in 0.5–1 percent of deliveries[113]. The left artery is absent in 59 percent of cases, the right in 41 percent. Prevalence is lower in African Americans (0.4 percent versus 1.2 percent for others), but their rate of associated congenital malformations (see below) is higher. SUA is approximately 15 times more common with chromosomal abnormalities[114]. However, SUA is rarely the only abnormality in such cases and routine karyotype is not recommended. There is a significant increase in the frequency of congenital malformations in karyotypically normal fetuses with SUA. While genitourinary anomalies (6.5 percent) and cardiac anomalies (6.3 percent) are most common, sirenomelia/caudal regression syndrome and limb-body wall complex are the most specific for SUA[115,116]. A relatively weak association of SUA with FGR and "pregnancy-induced hypertension" has been found in some studies[117].

The relative size of discordant umbilical arteries can range from small differences in diameter (hypoplasia) to near total atresia of one artery, and they can show different pulsatility indices by Doppler[118].

Apparent fusion of the 2 arteries mimicking SUA is sometimes seen in sections taken near the placental UC insertion site. This probably represents normal variation in the location of the Hyrtl anastomosis (see below), is relatively common by sonography (3.1 percent of pregnancies), and has no known clinical significance[119].

Proposed Pathogenesis: The UC normally transmits deoxygenated blood from the fetus to the placenta via paired umbilical arteries that arise from the internal iliac arteries, travel along the lateral margins of the bladder, and flank the urachus before entering the UC at the umbilicus. The umbilical arteries generally spiral around the umbilical vein before separating into 6–8 major chorionic arteries that send projections into the stem villi to perfuse the cotyledons. The two arteries communicate via the Hyrtl anastomosis in the distal UC within 3 cm of its insertion into the placenta. This anastomosis prevents major fetoplacental insufficiency in situations where one artery is lost or occluded during gestation.

Competing theories for Type 1 SUA are primary failure of the vasculogenic mesenchyme flanking the allantoic duct to form 2 functional arteries versus secondary involution of an initially normal vessel[48]. The common association with membranous UC insertion suggests that mechanical factors might result in preferential utilization of one umbilical artery and involution of the other[113]. This is one of several reasons why most authors favor early

variations in flow as the best explanation for most cases of Type 1 SUA.

Rare type II SUA are true malformations with an anomalous origin from the vitelline circulation in cases with deficient caudal development (acardiac fetuses, sirenomelia, and caudal regression syndrome)[120]. Persistent right umbilical vein represents failure of the right-sided member of the initially paired umbilical veins to involute in the UC and fetal abdomen.

Gross and Microscopic Features: SUA is easily recognized when only 2 vessels are observed on cut sections of the UC at the time of gross examination. Since focal involution and fusion near the placental insertion site are relatively frequent findings(see above), it is recommended that the UC be examined at both ends, serially sectioned at 5–10 cm intervals, and 2 sections flanking the middle 2/3 be submitted for histopathology. Careful histologic examination of all UC sections for a second hypoplastic or atretic artery should be performed in all cases with SUA at gross. Persistent right umbilical vein usually presents as 4 distinct muscularized vessels in a perpendicular section taken from a normal appearing area of the UC. Artifactual increases in the number of umbilical vessels can be seen in sections taken through areas with redundant folding of the UC (so called "false knots"). These areas generally should not be sampled.

Ancillary Diagnostic Testing: Not applicable.

Prognostic Implications: In one study 112 of 35,000 infants were found to have SUA at delivery; 17 percent of those with SUA had abnormal findings on initial renal ultrasound, and 42 percent of these persisted in subsequent studies. Vesicoureteral reflux was the most common anomaly, seen in 63 percent of the persistent cases[121]. While recurrence risk is generally low for SUA, other family members have an increased prevalence of genitourinary and GI anomalies suggesting a genetic component. Screening of first-degree relatives may be appropriate in some circumstances.

Knowledge Gaps: The pathogenesis of SUA (primary error of morphogenesis versus secondary vascular disruption) remains controversial. Whether there are genetic, epigenetic, or environmental risk factors is unknown.

Cystic and Solid Lesions (Allantoic Duct Remant/Cyst, Omphalomesenteric (Vitelline) Duct Remant/Cyst, Surface Epithelial Inclusion Cyst, UC Pseudocyst, UC Angiomyxoma, Vitelline "Hemangioma," Venous or Arteriovenous Malformations)

Definition: True cysts of the umbilical cord are lined by epithelium; transitional (rarely squamous or glandular) for *allantoic*, gastrointestinal for *omphalomesenteric (vitelline)*, simple squamous for *surface epithelial inclusions*[48]. *Pseudocysts* are mucoid-serous fluid filled cavities that lack an epithelial lining. A subset of pseudocysts arise adjacent to benign vascular proliferations that surround a major umbilical vessel and are termed "angiomyxomas"[122]. Smaller microscopic vascular proliferations without associated pseudocysts arise from small persistent vitelline vessels ("vitelline hemangiomas")[52]. Solid lesions are most common near the placental insertion site and include *venous and arteriovenous malformations.* Placental teratomas, also often located near the UC site, are discussed in Chapter 23.

Clinical Context: While not the focus of this chapter, fetal cystic lesions including patent urachus and small omphaloceles may extend into the UC through the umbilical ring. Extension of a patent urachus into the UC can be occult and present as a large urine-filled-UC, pseudocyst[123,124].

Cysts intrinsic to the UC are detected in 2–3 percent of first trimester ultrasounds[48,125]. Recognizable UC cysts in later pregnancy are much rarer and generally of no clinical significance. Isolated pseudocysts, are increased in aneuploid gestations, particularly trisomy 18[125].

Pseudocysts associated with angiomyxoma can be associated with elevated maternal serum alpha fetoprotein[126]. Venous or arteriovenous malformations can cause hydrops fetalis secondary to vascular shunting[48].

Proposed Pathogenesis: The allantoic duct is an extension of the urachus and provides scaffolding for the chorioallantoic circulation. The omphalomesenteric (vitelline) duct connects the fetal intestinal tract to the yolk sac and is accompanied by small

Figure 16.24 Umbilical cord pseudocyst. Segmental myxoid degeneration of the umbilical cord beginning approximately 3–4 cm from the placental insertion site.

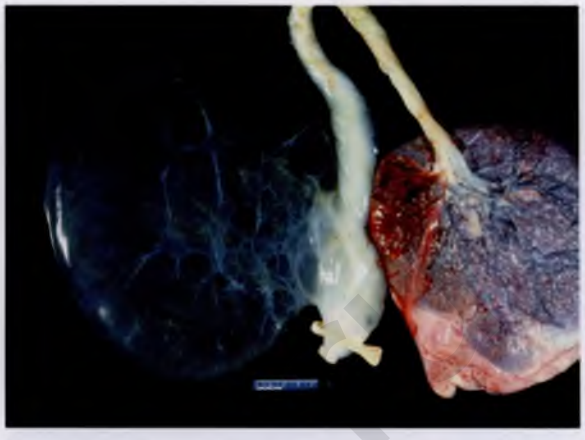

Figure 16.25 Umbilical cord angiomyxoma. A large pseudocyst (900 gm/25 cm diameter), exceeding the size and weight of the adjacent placenta, arises with a broad base from a fusiform vascular lesion in the mid-cord region.

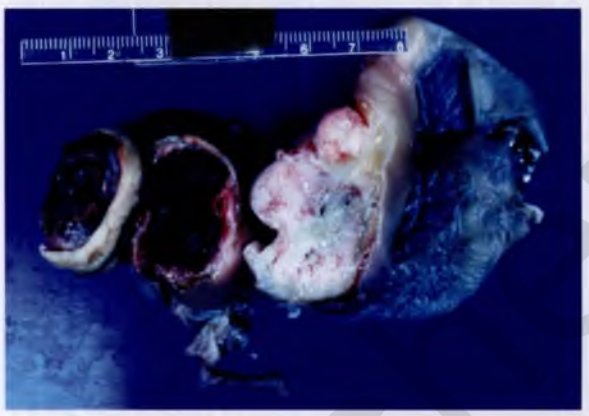

Figure 16.26 Umbilical cord venous malformation. Solid, partially hemorrhagic lesion arising from the placental umbilical cord insertion site.

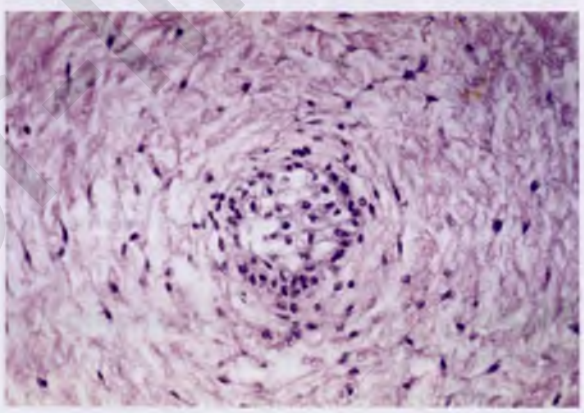

Figure 16.27 Allantoic duct remnant, umbilical cord. Vacuolated transitional-type epithelial lined, nonmuscularized duct remnant.

vitelline vessels that normally involute in early pregnancy. Both usually involute in later pregnancy but may persist as remnants or true UC cysts.

Isolated pseudocysts represent exaggerations of commonly encountered foci of liquefaction within Wharton's jelly. Pseudocysts associated with angiomyxoma represent transudation of fluid from the vascular component. Both angiomyxomas and vitelline hemangiomas directly arise from UC vessels, major umbilical vessels for the former and persistent vitelline vessels for the latter. Whether they represent tumors, malformations, hamartomas, or reactive proliferations has not been determined. Venous and arteriovenous malformations are poorly characterized, but resemble similar vascular lesions in children and adults.

Gross Features: True cysts of greater than 0.5 cm are usually visible by external inspection. Differentiation between a pseudocyst and focally edematous Wharton's jelly is somewhat arbitrary. Lesions measuring greater than 2 cm are considered worthy of note (Figure 16.24)[48]. Very large pseudocysts usually indicate an underlying vascular lesion (angiomyxoma, Figure 16.25)[126] The associated vascular component can be very small, so thorough sectioning of the base of the lesion is recommended. Venous or arteriovenous malformations are fusiform lesions that lack a cystic component (Figure 16.26). They are usually located at the placental insertion site and are solid to hemorrhagic on cross section[48].

Microscopic Features: Microscopic remnants of the allantoic duct are observed in up to 14.5 percent of term placentas and are usually located between the umbilical arteries (Figure 16.27)[127]. Cysts within

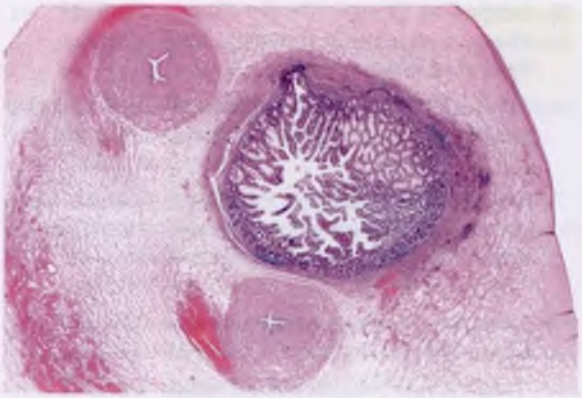

Figure 16.28 Omphalomesentereic (vitelline) duct cyst, umbilical cord. Small muscularized intestinal epithelial-lined cyst with surrounding necrosis.

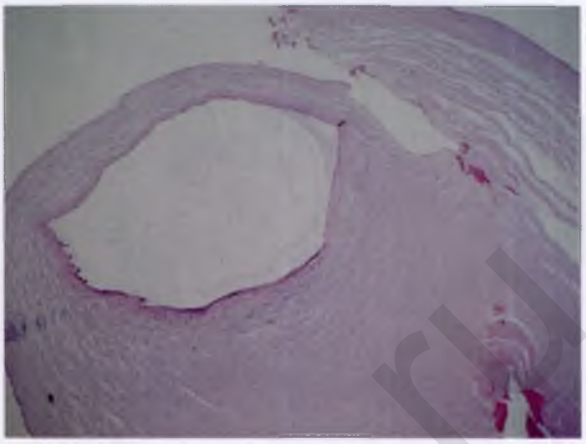

Figure 16.29 Surface epithelial inclusion cyst, umbilical cord. Simple squamous epithelial lined cyst located just below the umbilical cord surface.

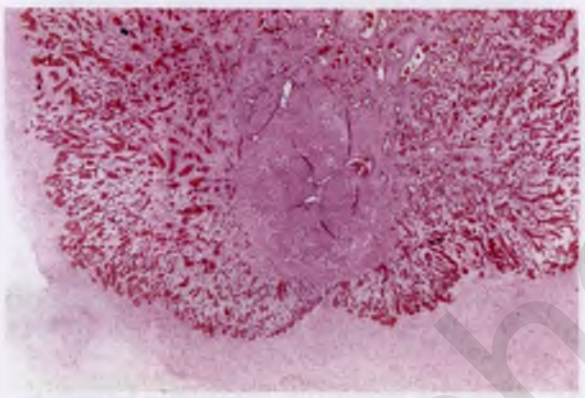

Figure 16.30 Umbilical cord angiomyxoma. Low power microscopic image from the same angiomyxoma shown in Figure 16.25 demonstrating clear origin from the umbilical arterial wall.

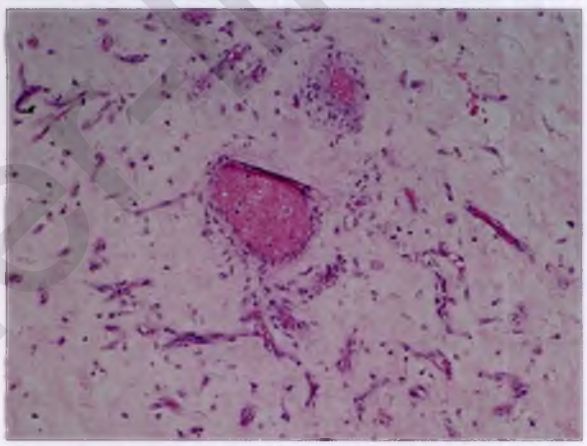

Figure 16.31 Vascular proliferation arising from vitelline duct remnant, umbilical cord (incidental finding). Small focus of branching angiogenesis surrounding 2 small, persistent vitelline vessels.

these remnants are uncommon and can be lined by transitional, squamous, or glandular epithelia. They generally lack smooth muscle, a feature useful in differentiating them from omphalomesenteric duct lesions. Remnants of the omphalomesenteric duct are seen in up to 1.4 percent of term placentas and have no consistent location within the UC. They are lined by intestinal-type mucinous epithelium and more commonly give rise to recognizable cysts than allantoic duct remnants (Figure 16.28). Surface epithelial inclusion cysts are lined by a simple squamous epithelium resembling amnion. They are incidental findings generally located just below the surface epithelium (Figure 16.29). Vascular proliferations associated with angiomyxoma are composed of an anastomosing network of small vessels surrounding a major umbilical vessel (Figure 16.30). Secondary hemorrhage, calcification, or ossification may be seen in some cases. Similar less extensive vascular proliferations without an adjacent cystic component arise from persistent vitelline vessels (Figure 16.31). Venous (or arteriovenous) malformations are larger vascular lesions lacking any clear association with an umbilical vessel (Figures 16.32). They are composed of thin-walled dilated vascular spaces lined by an attenuated layer of nonproliferative endothelium. Associated luminal thrombi are commonly seen.

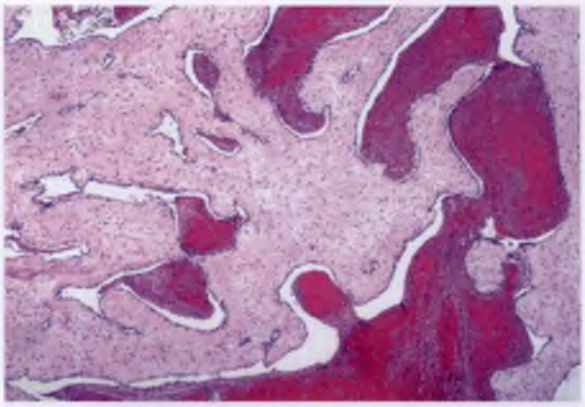

Figure 16.32 Umbilical cord venous malformation. Organizing recent thrombi within large ectatic, thin-walled vessels.

Ancillary Diagnostic Testing: not applicable.

Prognostic Implications: Cystic and solid UC lesions can in rare cases obstruct the fetoplacental circulation. Pseudocysts have been associated with aneuploidy, so careful examination of the neonate is warranted. Angiomyxomas may become sufficiently large to prompt elective preterm delivery. Venous or arteriovenous malformations can cause hydrops fetalis. In rare instances, rupture can lead to stillbirth[128]. In one case of UC vascular malformation, the delivered infant had a diffuse venulocapillary malformation (port wine stain)[129]. There is no known recurrence risk for any of these lesions.

Knowledge Gaps: The true nature of vascular proliferative lesions in the UC is unclear. Studies investigating their clonality would be of interest.

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Chapter 17

Perivillous Fibrin Deposition

Drucilla J. Roberts

Fibrin or fibrinoid is a common finding in term placentas, accumulating as patchy small foci usually at the margin of the placenta or under the chorionic plate. The material is a combination of organized blood-type fibrin and extracellular matrix proteins[1]. There may be a component of extravillous trophoblast derived major basic protein as well[2]. Perivillous fibrin(oid) (FND) is unusual in the first or second trimester and implies significant pathology. Increased perivillous FND can be separated into 2 pathological patterns: maternal floor infarction/massive perivillous fibrin deposition and perivillous fibrin plaque.

Maternal Floor Infarction / Massive Perivillous Fibrin Deposition (Massive Basal Plate Fibrin Deposition, Gitterinfarkt)

Definition: *Maternal floor infarction* (MFI)[3] is a distinctive lesion with marked increase in fibrin involving the maternal floor[3,4] covering at least 25 percent of the surface and enveloping the basal villi for ≥3 mm over the entire maternal floor on at least one slide[5,6]. Expansion of these lesions to involve the parenchyma proper (surrounding at least 50 percent of the villi in at least one slide[5,6] or 30 percent of the placenta grossly[7]) is termed *massive perivillous fibrin deposition* (MPFD). Many use the terms interchangeably, as the lesions likely represent a spectrum of the same pathogenesis.

Clinical Context: MFI/MPFD are rare lesions with an estimated incidence of <0.1 percent[8] to 0.5 percent.[4] The clinical correlates of MFI/MPFD include poor obstetrical history with losses, usually in the second and third trimester, intrauterine growth restriction (IUGR), intrauterine fetal demise (IUFD), or live birth with development of neurodisability. It appears that they can develop rapidly over the course of 3–4 weeks[9]. FND deposition is less common in early gestations, sometimes occurring due to medical abortion (Misoprostol) failures. When MFI/MPFD presents in early gestation (first to early second trimester), it is associated with recurrent miscarriage and prolonged vaginal bleeding[10]. Maternal characteristics of patients with MFI/MPFD include multigravidy, hypertension (any type), weight loss during pregnancy, a history of difficulty becoming pregnant[4], coagulopathies[11], enzyme deficiencies[12], and toxic exposures (cigarette smoke)[13], and I have personally seen a case with 5 pregnancies all showing MFI/MPFD in an alcohol-abusing mother). The fetus/infant is nearly always growth restricted and very often stillborn. Perinatal mortality rate is up to 40 percent[14]. There is a reported association with fetal renal disease (renal tubular dysgenesis[15] and cystic renal dysplasia[16]) and oligohydramnios[17]. A single case of MFI/MPFD with single umbilical artery and hypercoiled umbilical cord has been published[18]. Also reported are cases associated with mutations in the LCHAD (long-chain 3-hydroxyacyl-CoA-dehydrogenase) gene in the fetus/infant[15].

Proposed Pathogenesis: The etiology of MFI/MPFD is essentially unknown, but there are many associated clinical conditions (see above). Proposed underlying causes include increased fetal hydrostatic pressure leading to trophoblastic necrosis[16,18] and infections[19,20] (see Chapter 12). Redline et al.[9] discuss 3 hypotheses for pathogenesis:

1. Blood flow stasis related to inadequate perfusion or drainage from the intervillous space
2. Procoagulant effect, either trophoblast- or blood-derived
3. Trophoblastic pathology resulting in abnormal secretion of extracellular matrix proteins

MFI/MPFD may represent a single phenotype with many different underlying etiologies, both maternal and fetal.

Figure 17.1 Gross image of a placenta with maternal floor infarction (arrow on maternal floor). "Breadloafed" placenta reveals thickened maternal floor with yellow waxy fibin(oid) material (courtesy of B. Hargitai). Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

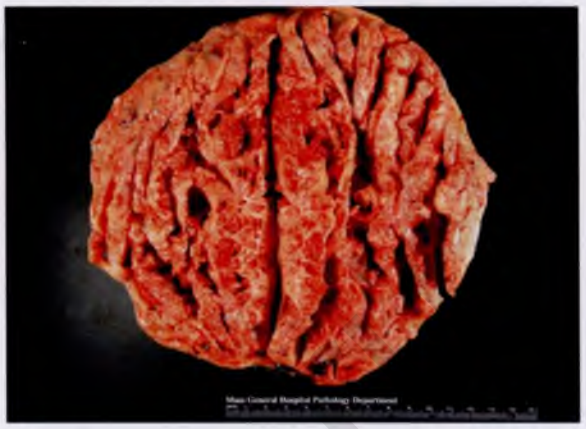

Figure 17.2 Gross image of a placental with massive perivillous fibrin deposition. The placenta is "breadloafed" and the yellow waxy fibrin(oid) material is evident throughout every cross section (also see Figure 17.3).

The most well-established risk factor for MFI/MPFD is maternal thrombophilia. In one series, more than 30 percent of cases of MFI/MPFD were associated with an identifiable maternal thrombophilia, either genetic or acquired – the most common being protein S deficiency[11]. Antiphospholipid antibody syndrome is another risk factor for the development of MFI/MPFD[21,22], as is protein C resistance[23]. The intervillous turbulence and relatively slow flow in the intervillous space is inherently coagulopathic[24], and any additional predisposition to clotting may promote the abnormal deposition of FND. Although theoretically attractive, genetic studies have failed to find any association with polymorphisms in genes encoding proteins involved in fibrinolysis[14]. The nature of the association with metabolic enzyme deficiency is less clear. Four cases of long-chain-3-hydroxyacyl coenzyme A dehydrogenase deficiency (LCHAD), either homozygous or compound heterozygous mutations, in infants with MFI/MPFD have been reported[12]. This important enzyme is involved in the beta-oxidation of long-chain fatty acids and has been associated with other disorders of pregnancy including acute fatty liver of pregnancy, preeclampsia, HELLP syndrome, and hyperemesis gravidarum[25]. LCHAD deficiencies in the fetus are thought to stress an already compromised maternal system, owing to maternal heterozygosity for LCHAD mutation, causing fatty acid oxidation intermediates to accumulate in the mother. By mechanisms not yet understood, these may contribute to the pregnancy specific pathologies described above including MFI/MPFD. Other fetal factors that may trigger MFI/MPFD include oligohydramnios or fetal vascular malperfusion which may act via changes in intrauterine hydrostatic pressure[16,18]. Redline et al. suggest that discordance for MFI/MPFD in dizygotic twins could indicate a fetal genotypic contribution[9]. Possible pathogenesis associated with an imbalance of pro- and anti-angiogenic factors in MFI/MPFD is discussed in Whitten et al[26]. In this study the authors show that levels of PIGF, sENG, and VEGFR are lower in cases with MFI/MPFD than in controls. In view of the significant recurrence risk, it has also been suggested that MFI/MPFD could be a manifestation of maternal rejection of the placental/fetal hemiallograft[3,6,27]. Maternal autoimmune diseases, such as polymyositis[28] have also been associated with MFI/MPFD[29].

Gross Features: MFI/MPFD placentas are distinctive. The MFI pattern has a thick band-like layer of fibrin (at least 3 mm diameter) along the "maternal floor." occupying at least 25 percent of the basal plate (Figure 17.1). The fibrin has an orange-rind look to it. This layer is firm and stands out on gross section, while the deeper/underlying parenchyma is softer and collapses when cut. Placentas with the MPFD pattern are diffusely firm and white (Figure 17.2). Cut surface shows marbling of the parenchyma with abundant white/orange FND (Figure 17.3). MFI/MPFD placentas tend to be small (<tenth percentile by weight). Often chorionic cysts are present below the chorionic plate, either grossly or microscopically[17].

Microscopic Features: The basal plate of MFI shows linear FND encasing several generations of villi leading to villous necrosis (Figure 17.4). There is often

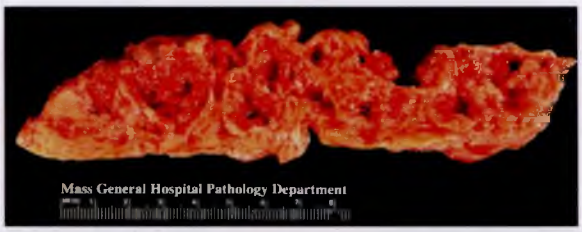

Figure 17.3 Single slice of placenta from Figure 17.2 showing transmural, thick anastamosing bands of fibrin(oid) in a placenta with massive perivillous fibrin deposition.

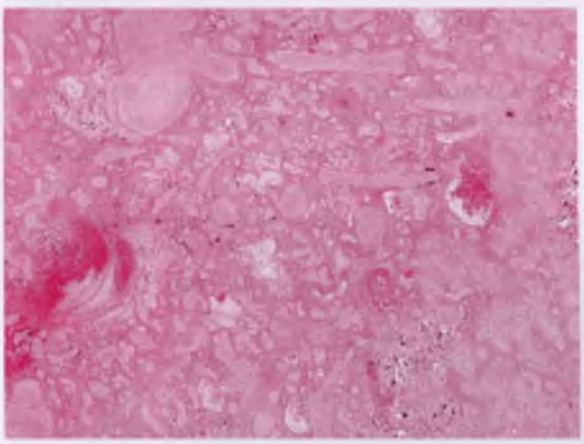

Figure 17.5 Massive perivillous fibrin deposition. Note near complete replacement of the intervillous space with fibin(oid) material.

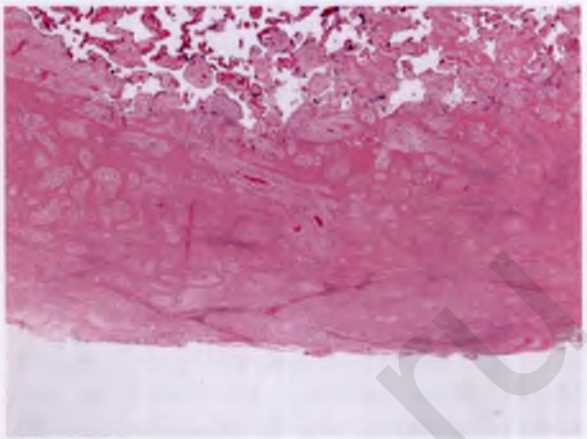

Figure 17.4 Photomicrograph of maternal floor infarct. Notice the thick band of fibrin(oid) material encasing many levels of villi across the maternal floor. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

associated deciduitis[8] with plasma cells[27]. The FND in MPFD is diffuse, either forming anastomosing bands or appearing confluent (Figure 17.5). It should occupy the majority of the placenta to make the diagnosis. If it is "regional," perivillous fibrin plaque (much more common; see below) should be favored. If there is a significant component of intervillositis, a diagnosis of chronic histiocytic intervillositis should be considered (see Chapter 15). MFI/MPFD should have minimal, if any, intervillositis. Other placental pathologies reportedly increased in cases of MFI/MPFD include single umbilical artery, decidual arteriopathy (see Chapter 5), accelerated villous maturation (see Chapter 7), and decidual necrosis[4,14].

Although there are no universally accepted guidelines, Katzman and Genest[5] have proposed criteria for the diagnosis of MFI (at least 3 mm of FND entrapping villi along the maternal floor in at least one microscopic slide) and for MPFD (more than 50 percent of the villi on a slide being encased in FND). We believe that in all cases suspected of MFI/MPFD by histology, the gross exam of the placenta should be reviewed by the pathologist if it wasn't previously personally visualized. We diagnose MFI/MPFD when at least 25 percent of the gross placental mass is affected, either the MFI alone or in MPFD. Correlation with the clinical history and fetal outcome is also necessary and often supportive of the diagnosis[30].

Ancillary Testing: Most ancillary testing is directed by additional clinical history, for example, PCR for enterovirus might be suggested if stillborn or neonatal death with autopsy showing myocarditis or with the suspicious maternal clinical history. Recurrent disease might warrant genetic testing, especially for LCHAD mutations in surviving infants or as part of the autopsy in losses. In view of the strong evidence for thrombophilia as an underlying cause in some cases[11], laboratory evaluation for such disorders may be appropriate. We also believe that any diagnosed or suspected case of MFI/MPFD should prompt a thorough review of all previous obstetric pathology specimens.

Prognostic Implications: Given the strong association with perinatal morbidity and mortality[31], all live births with this placental diagnosis should be closely monitored, especially for failure to thrive and neurodisability[32]. Consideration should be given for genetic testing for LCHAD deficiency especially in cases with neonatal/pediatric hypoglycemia. Preterm birth is common, present in up to 58 percent of cases[31]. Associated IUGR is present in up to

69 percent of cases and IUFD in 40 percent[35]. Future pregnancies should be monitored closely for recurrence. Published recurrence rates vary from 12[8], 14[5], 50[5]. to 78 percent[33]. It appears that the earlier in gestation that MFI/MPFD presents, the higher the recurrence rate[5], with the highest rate following those diagnosed in the first trimester.Some have noted elevated maternal serum AFP in pregnancies complicated by MFI/MPFD; potentially useful as a clinical marker for confirmation of diagnosis and monitoring for recurrence[34]. The lesion may be detected by antenatal ultrasound[17]. Although MFI/MPFD is often associated with catastrophic pregnancy complications, new clinical interventions (e.g. pravastatin therapy) may improve outcomes[35].

Knowledge Gaps: The etiology of MFI/MPFD is not well understood and further investigation of the hypotheses suggested above is needed. The only feature highly correlating with recurrence is diagnosis in the first trimester[5]. Additional pathologic features or ancillary tests better predicting recurrence risk are clearly worthy of investigation[16,36].

Perivillous Fibrin Plaque (Localized Perivillous Fibrin Deposition)

Definition: Mass-like area of increased FND; grossly visible, often at the margin of the placenta, and of insufficient extent for the diagnosis of MFI/MPFD.

Clinical Context: *Perivillous fibrin plaques* (PFP) are common findings in term placentas and are typically of no clinical significance unless the placenta is small, in which case they may be associated with placental insufficiency and fetal growth restriction[37]. The prevalence of PFP is about 20 percent at term, but lower in preterms (6 percent)[38]. They are less common in placentas from pregnancies complicated by hypertension or diabetes[7] and more common in "idiopathic" IUGR. They can be related to CMV infection[39] (see Chapter 12).

Proposed Pathogenesis: Two hypotheses exist. One is primary damage/necrosis of the villous syncytiotrophoblast, leaving the villous stroma or trophoblastic basement membrane exposed resulting in platelet aggregation and fibrin deposition which "grows" causing a mass of fibrin with necrotic villi in the center (the Eden hypothesis[40]). The other is that local alterations in maternal perfusion result in turbulence and/or reduced flow causing fibrin deposition

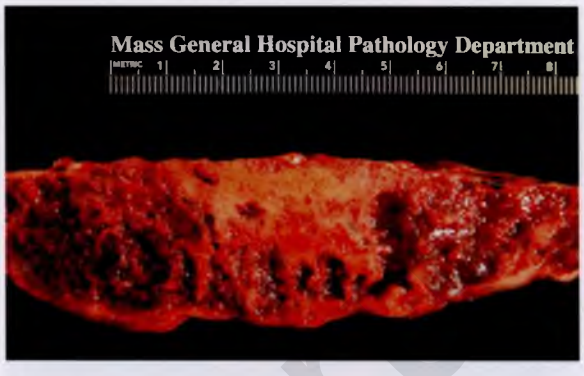

Figure 17.6 Gross image of a perivillous fibrin plaque.

with secondary necrosis of the trophoblast and eventually "suffocation" of the villi and villous necrosis[7]. We favor the second theory as the first leaves some questions about what causes trophoblastic damage and is counter to the decreased prevalence in hypertensive and diabetic pregnancies – two pathologies with documented evidence of increased trophoblastic damage[41].

Gross Features: Firm homogeneous masses, often at the margins of the placenta, with a smooth rubbery texture and a yellow/orange color (Figure 17.6). PFP vary millimeters to centimeters in dimension and may be irregular in shape. PFPs are usually sharply demarcated from the surrounding villous tissues. They may be associated with intervillous thrombi (see Chapter 11), but not usually with typical placental infarcts.

Microscopic Features: The magenta or light pink FND in the intervillous space surrounds villi that are usually in the process of degenerating due to "suffocation" (Figure 17.7). Often, intraplacental-type extravillous trophoblast are prominent within the fibrin (Figure 17.8). The entrapped villi are widely separated from each other by the FND (contrasting with the abutting necrotic villi seen with placental infarcts, see Chapter 7). Occasionally, there is associated dystrophic calcification (Figure 17.9).

Ancillary Testing: Consideration of CMV infection, primary or recurrent, may prompt immunohistochemical staining, maternal/fetal serology, or fetal viral culture in some cases[39].

Prognostic Implications: PFP are benign lesions, when found in term placentas of appropriate size/weight. When present in abnormally small or preterm placentas they may decrease placental reserve enough

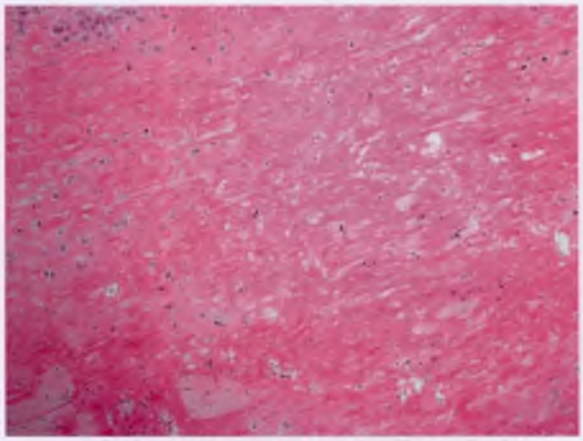

Figure 17.7 Histologic image of perivillous fibrin plaque. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

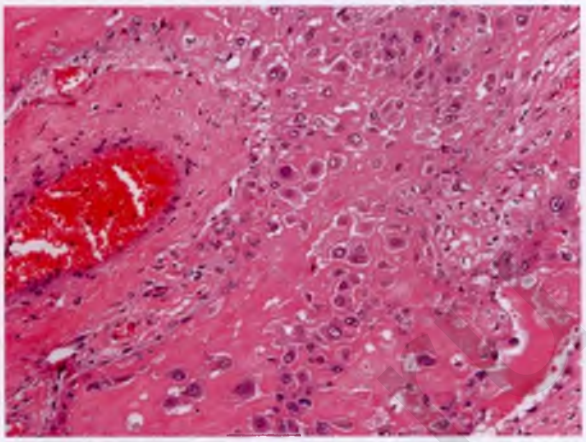

Figure 17.8 Perivillous fibrin plaque with proliferation of intraplacental-type extravillous trophoblast.

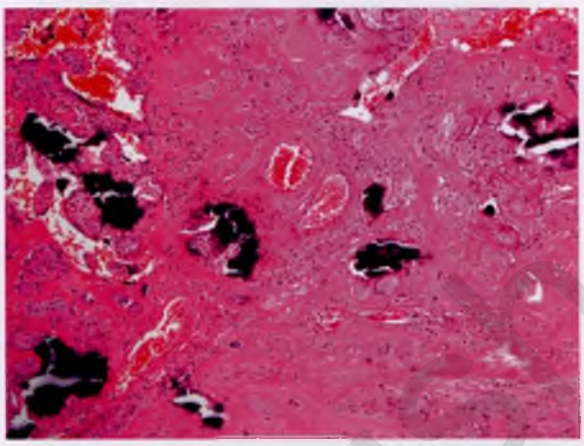

Figure 17.9 Perivillous fibrin plaque with dystrophic calcification. Image provided with permission by D. Roberts, Massachusetts General Hospital, Boston, MA.

to result in fetal hypoxia and IUGR[37,39]. Rare cases associated with congenital CMV have potential morbidity including neurodisability, hearing and visual loss[42,43] (see Chapter 12).

Knowledge Gaps: The pathogenesis of PFP remains unclear. Further investigation is required to distinguish between the hypotheses of trophoblast damage[40] and intervillous turbulence[7].

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Chapter 18

Atypical Intraplacental Hemorrhages / Thrombi

Brendan Fitzgerald and Sarah Keating

Massive Subchorial Thrombohematoma (Massive Subchorionic Thrombohematoma, Subchorionic Tuberous Hematoma, Breus' Mole)

Definition: *Massive subchorial thrombohematoma* is defined as a substantial collection of clotted blood in the intervillous space, immediately beneath the chorionic plate. The degree of collection is such that the chorionic plate and placental villous parenchyma become separated and the chorionic plate surface is often distorted and nodular. While there is no agreed definition of what constitutes a "massive" thrombohematoma, typical cases are easily recognized as they may involve significant portions (e.g. 25–50 percent) of the total placental mass. Alanjari et al. defined a massive subchorial thrombohematoma as being greater than 1 cm in thickness with ≥50 percent involvement of the fetal surface of the placenta[1].

Clinical Context: Massive subchorial thombohematomas are relatively rare. Incidence has been reported as between 1:1887 and 1:3133[2,3]. Breus originally described a placental lesion, "subchorionic tuberous hematoma," with multiple blood filled sacculations in 1892[4]. He thought that they were a consequence of the persistence of intervillous blood flow after intrauterine fetal death. Over time, association of these lesions with live births and antenatal ultrasound diagnosis has confirmed that they develop during fetal life. They are associated with various pregnancy complications, including intrauterine growth restriction, oligohydramnios, antenatal hemorrhage, preterm delivery, intrauterine fetal death, pulmonary hypoplasia, and neonatal death[1,5,6]. An association with monosomy X and partial mole have been reported[7,8]. Maternal features have included circulatory disorders, thrombophilia[9], hypertension, and diabetes. Many of these lesions are now recognized antenatally due to detection of sonographic abnormalities of placental size, thickness, and texture in complicated pregnancies[1,10,11]. Doppler assessment of flow through the lesion and magnetic resonance imaging (MRI) may assist in definitive diagnosis[11–13].

In interpreting the literature on its various clinical associations, the pathological lesion defined here as subchorial thrombohematoma needs to be distinguished from the radiologic "subchorial hematoma." In obstetric ultrasonography the term "subchorial hematoma" is used to describe hemorrhage between the uterine wall and the membranes or placental disc[14,15]; these would be described pathologically as extra- or retromembranous, marginal, or retroplacental hemorrhages (see Chapter 8). In rare cases marginal hematomas may extend below the chorionic plate, forming a lesion resembling massive subchorial thrombohematoma.

Proposed Pathogenesis: There is no consensus on how or why massive subchorial thrombohematomas form. They may be a final common result of a number of abnormalities, all of which increase the risk of accumulation of thrombohematoma at this specific site. By molecular techniques, the thrombohematoma has been shown to be predominantly maternal in origin in one case[16], and thus appears to be a gross exaggeration of the minimal fibrin deposition that occurs on the undersurface of the chorionic plate in normal pregnancies. An association with thrombophilia may suggest a prothrombotic tendency in some cases[9], but indirect mechanisms may also be at work. Associations with monosomy X and partial mole[7,8] suggest that abnormal villous development may have a role; in this situation, abnormal villous morphology may increase turbulence or obstruct flow, resulting in thrombohematoma formation. Abnormally small and thick placentas have been associated with adverse pregnancy outcomes. One hypothesis suggests that this abnormal thickness is due to placental maldevelopment, villous hypoplasia and reduced structural

Figure 18.1 Massive subchorial thrombohematoma. The fetal aspect of the disc has multiple bulges; some chorionic vessels have become buried within surface folds.

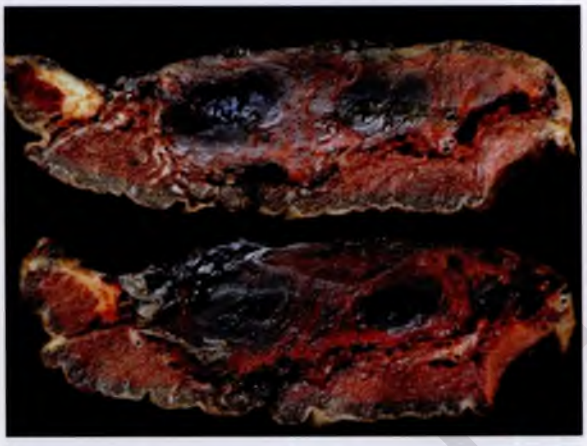

Figure 18.2 Cross section of a massive subchorial thrombohematoma. Thrombohematoma occupies more than 50 percent of the disc thickness, with multiple laminations. Image provided with permission by S.M. Jacques, Hutzel Women's Hospital, Detroit Medical Center, Detroit, MI.

integrity so that the placenta abnormally "inflates" under the pressure of maternal blood in the intervillous space[17]. It may be that some of these structurally abnormal placentas have abnormal spaces beneath the chorionic plate in which flow is turbulent and thrombohematoma may accumulate. In one study of massive subchorial thrombohematomas, 2 of 14 cases had diffuse distal villous hypoplasia[11].

Gross Features: Small accumulations of fibrin and small thrombi (subchorionic intervillous thrombi) are commonly seen in the subchorionic region of the placenta and these increase in frequency with gestational age. However, large accumulations at this site are unusual. The placenta at pathologic examination is likely to be thicker than normal as a result of the accumulation of thrombohematoma beneath the chorionic plate. The fetal surface tends to be discolored due to both the presence of the underlying thrombohematoma but also due to the presence of chorionic plate hemosiderin. The thrombohematoma accumulation separates the chorionic plate from the bulk of the villous parenchyma, save for the major stem villi which traverse the lesion. As the lesion may not be evenly distributed and because of the tethering effect of anchoring villi, the chorionic plate is pushed toward the amniotic cavity in multiple irregular bulges or nodules. Such bulging may have the effect of "burying" the chorionic plate vessels or the umbilical cord insertion (Figure 18.1). On sectioning of the placenta, the lesion is characterized by a thick layer of laminated thrombus immediately beneath the chorionic plate (Figure 18.2). In stereotypical examples this layer may comprise 50 percent or more of the placental thickness. Only an occasional stem villous may be seen traversing the main areas of thrombohematoma accumulation. In some examples there may be a conspicuous looseness to the placental texture in the subchorionic region of the placenta adjacent to the lesion.

Microscopic Features: Microscopically the thrombohematoma is typically laminated and complex. There may be evidence of thrombus deposition of varying ages. Scattered hemosiderin laden macrophages may be seen both within the lesion and in the overlying chorionic plate and membranes. The background placenta may show other pathologic lesions such as those of maternal vascular malperfusion and distal villous hypoplasia (see Chapters 6 and 7).

Differential Diagnosis. Subchorionic intervillous thrombi are a common finding in placentas, particularly toward term. These are generally small plaques, < 1 cm in thickness, with no evidence of significant chorionic plate distortion. On occasion, subchorionic intervillous thrombus formation may be unusually prominent, but a diagnosis of "massive subchorionic hematoma" may not be warranted. In such situations a descriptive approach and discussion seems practical (Figure 18.3). Acute retroplacental hematomas, at the disc margin, may extend from the disc edge beneath the chorionic plate, particularly at earlier gestational ages. Clinically these may be seen in the context of ascending infection in the second trimester. The

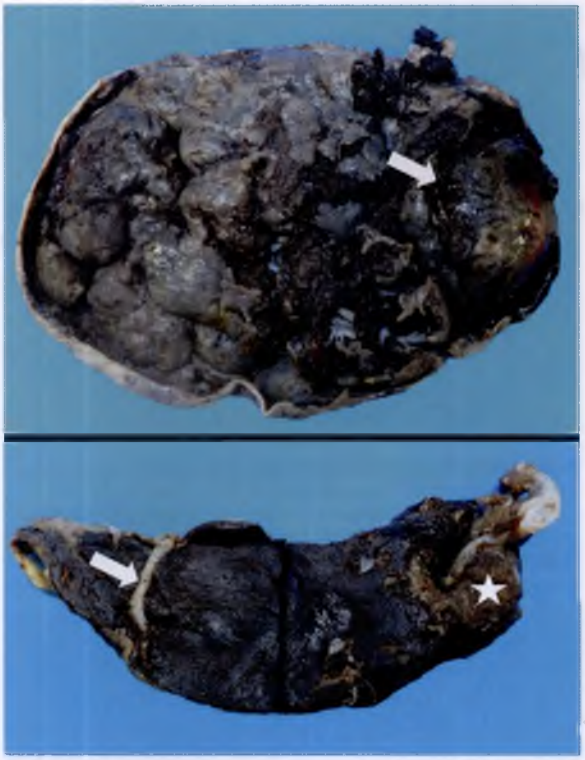

Figure 18.3 Unusual subchorial thrombohematoma at the edge of a placental disc (arrow). On cross section of the lesion (lower image), stem villi clearly cross the area of thrombohematoma (arrow) as it occupies the full thickness of the disc. Normal terminal villous development is evident at the lesion edge (star) but not within the thrombohematoma. Examples such as this may suggest that impaired villous development has a role in formation of some of these lesions; it is also an example of a lesion where it may be debated whether it is truly a "massive" thrombohematoma.

clinical context, peripheral location, lack of chorionic plate distortion and absence of chronicity (lack of hemosiderin deposition, discoloration, etc.) are distinguishing features.

Ancillary Diagnostic Testing: Massive subchorial thrombohematoma is primarily a gross diagnosis that generally does not require ancillary diagnostic techniques. However, in some clinical and pathologic situations, confirmation of diagnoses such as partial mole or monosomy X may be required. In the context of pregnancy loss, maternal thrombophilia testing is often undertaken, irrespective of the placental diagnosis, but with a surviving neonate there is no current standard recommendation.

Prognostic Implications: When identified antenatally, massive subchorioal thrombohematomas are associated with a high rate of fetal growth restriction and fetal or neonatal death. In a report of 14 cases identified over an 8 year period, there were only 7 survivors; the remainder succumbed to neonatal death, intrauterine fetal death, or termination of pregnancy[1]. The non-survivors were more frequently characterized by extreme preterm delivery and severe intrauterine growth restriction. In this study, survival was associated with normal growth and normal umbilical artery Doppler findings. Other reports also indicate high rates of fetal or neonatal death[2,3]. It remains to be determined whether increasing antenatal diagnosis will have a significant effect on fetal/neonatal outcome.

Knowledge Gaps: Due to their rarity, there are no large studies that have assessed the combined maternal, fetal, and placental characteristics of these thrombohematomas, and the etiology of remains inadequately understood. To fully characterize their pathogenesis, we need a better understanding of the in utero evolution of these lesions over time. This would be facilitated by early diagnosis or through detecting at risk pregnancies through abnormalities of maternal serum screening and/or ultrasound imaging[18,19]. MRI evaluation may be needed to adequately visualize the lesions themselves. A better understanding of possible contributory prothrombotic factors in larger series of cases is also required. Detailed morphological studies of the potential structural pathology of affected placentas, e.g. using stereologic techniques, may clarify whether there is a role in primary abnormal development. Importantly, the reporting of associated pathology, within the parenchyma of placentas containing massive subchorial thrombohematomas, might further our understanding of lesional evolution.

Subchorionic Intervillous Thrombus / Hematoma (Subchorionic Fibrin Plaque, Chronic Subchorionic Hematoma)

Definition: *Subchorionic intervillous thrombi/hematomas* are defined as small collections of clotted blood in the intervillous space immediately beneath and adherent to the chorionic plate. They are usually less than 1 cm in thickness. They do not significantly distort the chorionic plate, presenting as pale tan plaques visible though the fetal aspect of the disc, or as red/purple, pale or laminated subchorionic lesions in placental cross sections.

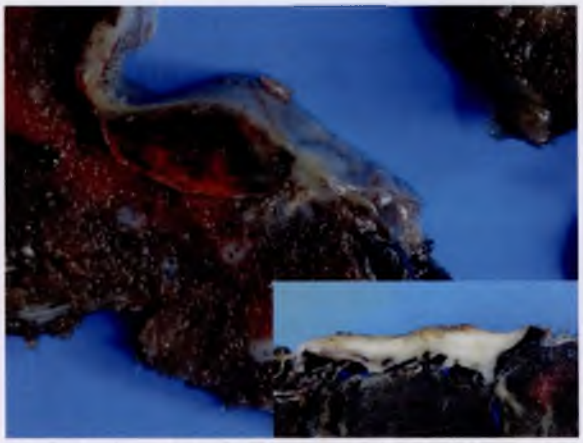

Figure 18.4 Gross appearance of a subchorionic intervillous thrombus (main image). The lesion is clearly adherent to the undersurface of the chorionic plate, with laminations parallel to the plate itself. The inset image is an older lesion that is pale and firm; laminations are still evident on microscopy.

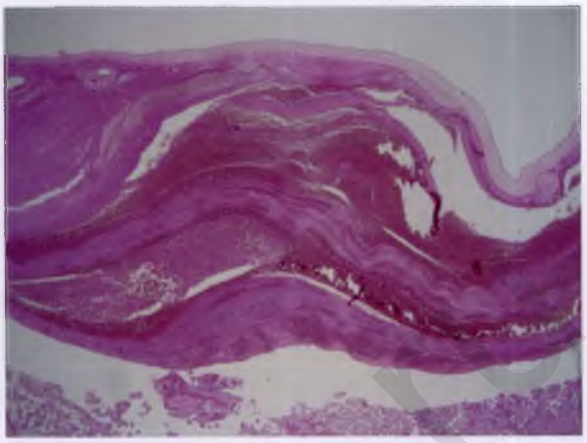

Figure 18.5 Low power view of a subchorionic intervillous thrombus with alternating bands of maternal erythrocytes and fibrin.

Clinical Context: There is significant variability in the number and size of subchorionic intervillous thrombi present at pathologic placental examination. In most cases, they are an incidental finding in placentas submitted for a variety of clinical indications. In the infrequent cases where thrombi are unusually large or numerous, there is potential for clinical overlap with massive subchorial thrombohematoma. The latter is only distinguished from subchorionic intervillous thrombi by the extent of clotted blood.

Proposed Pathogenesis: As the placenta forms, the maternal (intervillous) aspect of the chorionic plate has a layer of cytototrophoblast and syncytiotrophoblast covering the chorionic mesoderm. With time, in all placentas, a layer of fibrin(oid) material begins to accumulate at this site (Langhan's stria), composed of a mixture of "fibrin-type" and "matrix-type" fibrin(oid) with admixed extravillous trophoblasts. As the fibrin(oid) increases in quantity it may become visible through the fetal surface of the disc as a tan patch or plaque. The amount of this material varies greatly, even in normal pregnancies. In addition to this fibrin(oid) accumulation, small laminated thrombi may form on the maternal aspect of the chorionic plate that may be termed subchorionic intervillous thrombi. Such small subchorionic intervillous thrombi likely form beneath the chorionic plate as a result of stasis or turbulence of blood flow in the maternal circulation at the roof of the intervillous space. Blood entering the intervillous space circulation at the center of the placentome is directed toward the chorionic plate, where it is then deflected back toward the basal plate. Any irregularities in the maternal side of the chorionic plate may therefore lead to turbulence or syncytiotrophoblast injury and formation of small thrombi.

Gross Features: Fibrin(oid) is evident beneath the fetal surface of the disc as tan or purple/tan patches. This is in contrast to the normal amount of fibrin(oid) material, which is fairly subtle in appearance. Patches vary from small specks to large confluent plaques; their extent varies greatly from case to case. There is some overlap between the deposition of fibrin(oid) beneath the chorionic plate and the formation of true laminated thrombi. From the fetal surface they may be indistinguishable, or the true thrombi may be darker and tan/purple depending on the amount of red cells still present within them. Subchorionic intervillous thrombi appear as laminated lesions adherent to the chorionic plate at the roof of the intervillous space (Figure 18.4). When fresh they are hemorrhagic and dark in color and as they age laminations may be more obvious before they eventually become progressively paler and less obviously laminated.

Microscopic Features: The appearance varies depending on the age and relative amount of fibrin and red cells present. They consist of laminated thrombi that appear to be primarily adherent to the chorionic plate (Figure 18.5). As they age, hemosiderin-laden macrophages may be present and there may be a small amount of hemosiderin deposition in the overlying chorionic plate. Organization of these lesions has not been reported. A practical point highlighted by Kaplan

is that plaques of subchorionic fibrin or subchorionic intervillous thrombi may provide a barrier to passage of maternal inflammatory cells and selective selection of areas with fibrin-plaques or thrombi may result in underestimation of maternal response to infection[20]. This should be borne in mind when sampling placentas for diagnostic purposes.

Differential Diagnosis. These lesions need to be distinguished from typical centrally located "intervillous thrombi" (see Chapter 11) that can occur anywhere in the placental parenchyma, and occasionally in the vicinity of the chorionic plate. When these are present near the chorionic plate they maintain their typical angulated shape, without the primary appearance of adherence to the plate itself. Fibrin(oid) material normally accumulates beneath the chorionic plate; however, in some instances, e.g., ischemia or chronic villitis, fibrin(oid) accumulation may be excessive. Such areas of excess fibrin(oid) deposition in the placental parenchyma may be present near the chorionic plate and therefore be visible grossly from the fetal surface. Infarcts may also be visible in this manner. Other focal lesions such as chorangiomas can also present in the subchorial zone. As previously stated, massive subchorial thrombohematoma is separated from subchorionic intervillous thrombi mainly by extent. Generally there is no difficulty in separating them, as the extent of thrombohematoma formation is dramatic in massive subchorial thrombohematoma. However, given the potential for a continuum between the two lesions, some cases may require narrative reports with consideration of findings in the rest of the placenta and associated clinical details for interpretation of significance (Figure 18.3).

Ancillary Diagnostic Testing: Not required.

Prognostic Implications: Occasional small subchorionic intervillous thrombi are a common finding in many placentas and are of doubtful clinical significance or impact. If they are unusually large or numerous, consideration may be given to the possibility that there were potential reasons for the excessive thrombus formation, either structural, due to abnormal flow or prothrombotic tendency. In these situations, the combined assessment with other features in the case can aid in potential prognostic implications.

Knowledge Gaps: Small subchorionic intervillous thrombi are common and there is no clear definition of how extensive or numerous these lesions should be in order to be considered pathologic Future studies may help clarify this issue.

Basal Intervillous Thrombus / Hematoma

Definition: *Basal intervillous thrombi* are intervillous thrombi that are defined by their position adjacent to the basal plate. They have been described as lesions of 2–5 cm, often in a paraseptal location. When acute, they may be red, soft and ovoid, with or without laminations, becoming paler and more firm as they age[21].

Clinical Context: Basal intervillous thrombi have been described as incidental lesions in normal mature placentas, with increased frequency in pregnancies complicated by maternal hypertension, preeclampsia, and maternal thrombophilias[21].

Proposed Pathogenesis: These lesions are proposed to be related to thrombosis of maternal decidual veins[21], though other etiologies such as retroplacental hemorrhage with oblique intraplacental extension should be considered.

Gross Features: Apart from the defining characteristics above there are no other specific features.

Microscopic Features: Fresh examples are described as showing fibrin laminations admixed with erythrocytes of maternal origin. The underlying decidua may be necrotic[21].

Ancillary Diagnostic Testing: None.

Prognostic Implications: When single or few, they are reported to be insignificant, but when multiple, they are thought to represent markers of maternal hypertensive disorders or thrombosis[21].

Knowledge Gaps: The precise relationship between basal intervillous thrombi, classic centrally located intervillous thrombi, rounded intraplacental hematomas, and infarction hematomas requires further clarification (see discussion on the rounded intraplacental hematoma section below).

Rounded Intraplacental Hematoma (Centrally Hemorrhagic Villous Infarct, Infarction Hematoma)

Definition: A *rounded intraplacental hematoma* is defined as a hematoma occurring within the placental

parenchyma having a round shape or a number of rounded areas. It characteristically abuts the basal plate and in most instances is surrounded by a rim-like area of placental infarction[22].

Clinical Context: Reported associations include maternal hypertension, preeclampsia, HELLP syndrome, gestational diabetes, intrauterine growth restriction, preterm delivery, and fetal loss[22,23].

Proposed Pathogenesis: Rounded intraplacental hematomas are proposed to form as a result of rupture of vasculopathic maternal decidual arterioles[22]. In the authors' opinion there is a close etiological relationship between these lesions and a subset of retroplacental hematomas, the only difference being the precise site of compromised vascular integrity and the direction of the resulting hemorrhage and hematoma accumulation. We would suggest that rupture of a vasculopathic vessel would lead to sudden exposure of a highly localized area of the intervillous space to pressure approaching that in spiral arterioles. This in turn would lead to a rapid focal expansion of the intervillous space and an expanding rounded "hematoma." Compression of the surrounding villi may then have the effect of naturally controlling the hemorrhage, with this compressed rim then undergoing secondary ischemic infarction. Alternatively, thrombosis occurring in the vasculopathic vessel of origin may also limit its extent. A related, possibly identical lesion – infarction hematoma or centrally hemorrhagic villous infarct – is discussed in Chapter 7 (also see below).

Gross Features: Very occasionally, large examples have been observed to displace the chorionic plate, resulting in bulging and discoloration of the fetal surface. Also, on occasion, prominent pits have been observed on the maternal surface at points of apparent origin of these hemorrhages. In most instances however the lesion is only visible when the disc is sectioned and the cut surface is examined. On cut surface of the placenta, the gross appearance will depend on the lesion age (Figure 18.6). Nearly universally, the lesion clearly abuts the basal plate of the disc, which is an important diagnostic clue to its etiologic nature. Very fresh examples consist of what is usually a simple rounded area of hemorrhage that displaces and compresses the surrounding placental parenchyma. More complicated examples may demonstrate multiple branching areas of rounded

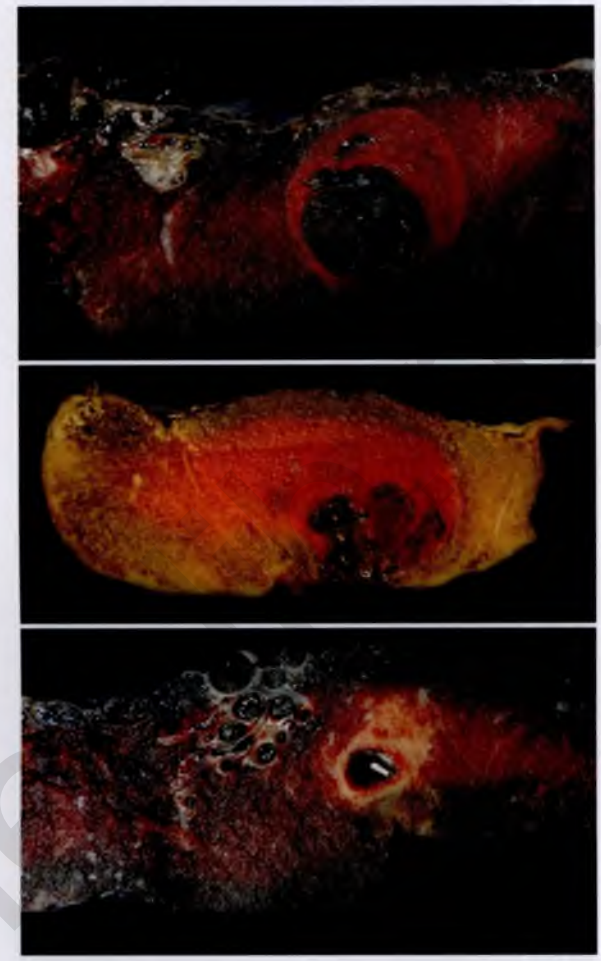

Figure 18.6 Variable appearances of rounded intraplacental hematomas (RIHs). The upper panel shows a relatively fresh RIH with surrounding infarction (mainly toward the chorionic plate side). In the middle panel a complicated, branching RIH is associated with a large area of overlying infarction. The lower panel has an old RIH that appears "scar-like" with central degenerating hematoma.

hemorrhage that appear to emanate from a common point of origin at the basal plate. Occasionally, small examples may be entirely located within in the basal plate region. With time, the rim of compressed parenchyma surrounding the hematoma shows increased pallor and firmness, corresponding to evolving infarction. In some examples the infarction associated with the hematoma is asymmetrical, with an area of infarction fanning out between the basally positioned hematoma and the overlying chorionic plate. Ultimately the central hemorrhage degenerates and old lesions then consist of a cyst-like space containing degenerating blood with a surrounding rim of pale, firm, infarcted parenchyma. The lesions may be single

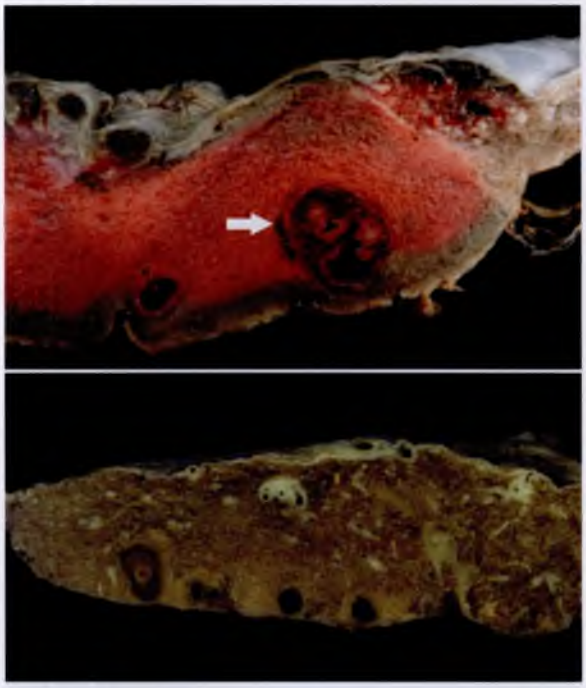

Figure 18.7 In the upper panel there is a recent RIH with irregular laminations; there is no surrounding infarction. In the lower panel the tendency of RIHs to occur along the basal plate is clearly evident. Again, some of the examples in the lower panel have little or no associated infarction. Image provided with permission by S.M. Jacques, Hutzel Women's Hospital, Detroit Medical Center, Detroit, MI.

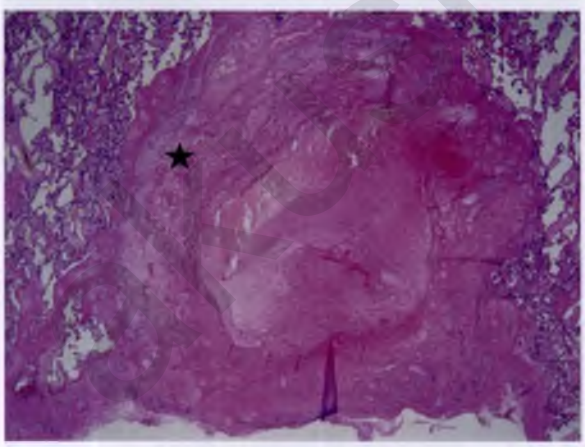

Figure 18.9 Old, rounded intraplacental hematoma. There is some collapse of the lesion and some loss of the rounded shape. The surrounding rim of infarction, fibrin(oid) deposition and extravillous trophoblast proliferation is well developed (star). Image provided with permission by S.M. Jacques, Hutzel Women's Hospital, Detroit Medical Center, Detroit, MI.

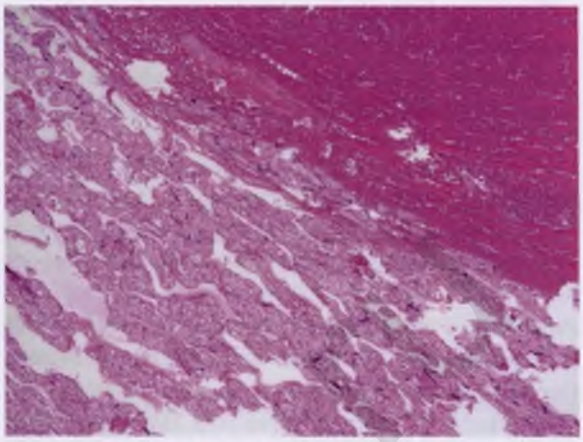

Figure 18.8 Edge of a fresh, rounded intraplacental hematoma showing some compression but no infarction of the adjacent parenchyma.

or multiple (Figure 18.7). As the proposed pathogenesis is related to decidual vasculopathy, other lesions associated with maternal vascular malperfusion or loss of maternal vascular integrity may be seen such as "conventional" placental infarcts, areas of increased perivillous fibrin(oid), and/or retroplacental hematomas.

Microscopic Features: Centrally, fresh lesions consist of non-laminated areas of hemorrhage. If laminations are present, they tend to be few, often curved, and seem to broadly follow the line of the lesion's edge. The immediately adjacent parenchyma shows compression of the villous parenchyma with resultant loss of the intervillous space (Figure 18.8). Coexisting ischemia leads to villous trophoblast injury, fibrin(oid) deposition and villous agglutination, with resulting formation of a ring-like rim of surrounding infarction (Figure 18.9). As mentioned, infarction may extend away from the lesion toward the chorionic plate. In some instances, depending on how the lesion is sampled, dilated and/or vasculopathic decidual arterioles may be seen in the basal plate immediately beneath the lesion. The background placental parenchyma may show other evidence of maternal vascular malperfusion such as accelerated villous maturation, distal villous hypoplasia, increased perivillous fibrin(oid) or "conventional" placental infarction.

Differential Diagnosis: Centrally located intervillous thrombi may be distinguished from rounded

hematomas by the fact that intervillous thombi tend to be rhomboid and angulated, with at least some relatively straight borders (instead of round), display prominent parallel laminations, and show displacement but little or no compression of the surrounding villi. Occasionally, hemorrhage may occur into placental septae/septal cysts and so also present as basally located hemorrhages. The relationship to placental septae overlying these lesions and lack of other features typical of rounded intraplacental hematomas (round shape, infarcted rim) should allow easy separation. Infarction hematomas and basal intervillous thrombi are discussed below. On gross examination, intraplacental choriocarcinoma may be infarct-like and show central areas of tumor necrosis, potentially mimicking the appearance of an old rounded intraplacental hematoma.

Ancillary Diagnostic Testing: None are required for pathological diagnosis. Currently no specific maternal ancilliary testing is indicated.

Prognostic Implications: In the 13 cases originally reported, there was a high frequency of severe intrauterine growth restriction, premature delivery (mean of 30 weeks) and maternal hypertensive disorders. Two terminations of pregnancy were conducted for previable severe intrauterine growth restriction. Rounded intraplacental hematomas thus appear to be associated with significant pregnancy complications[22]. In a report on 26 further examples there was a statistically significant increased incidence of stillbirth in placentas with rounded intraplacental hematomas when compared to placentas showing evidence of maternal vascular malperfusion without rounded intraplacental hematomas[23]. Recurrence of rounded intraplacental hematomas in subsequent pregnancies has also been documented[23]. Interestingly, there may be an opportunity for antenatal diagnosis of this type of lesion using ultrasound[24]. This potential for antenatal diagnosis could have an impact on how these pregnancies are managed, and as our knowledge of prognosis evolves, the potential for a positive impact on pregnancy outcome.

Knowledge Gaps: Descriptions of rounded intraplacental hematoma and infarction hematoma[25] (Chapter 7) appear to be very similar from the descriptions in their original reports, and in the authors' opinion they may represent the same pathologic lesion. Further work is necessary to clarify this issue. Similarly, basal intervillous thrombi described above share some morphological and clinical features with both rounded intraplacental hematomas and centrally located intervillous thrombi. In the original description of rounded intraplacental hematomas, they were in fact separated out from a group of placentas with lesions originally reported as basally located "intervillous thrombi." Again, further work is required to determine whether there is a reproducible category of placental lesion separate from rounded intraplacental hematoma and centrally located intervillous thrombus, that may be termed a basal intervillous thrombus. As rounded intraplacental hematomas have been only recently described, further studies are required to increase the number of reported cases and to further investigate their clinical associations.

Basal Plate Plaque

Definition: A *basal plate plaque* is defined as a pale plaque-like lesion on the intervillous space side of the basal plate (Figure 18.10). It is composed of spindle cells in a loose, myxoid-appearing stroma, with the spindle cells generally arranged parallel to the basal plate (Figure 18.11). It forms as a result of organization of fibrin/thrombus, with subsequent replacement by myofibroblasts[26].

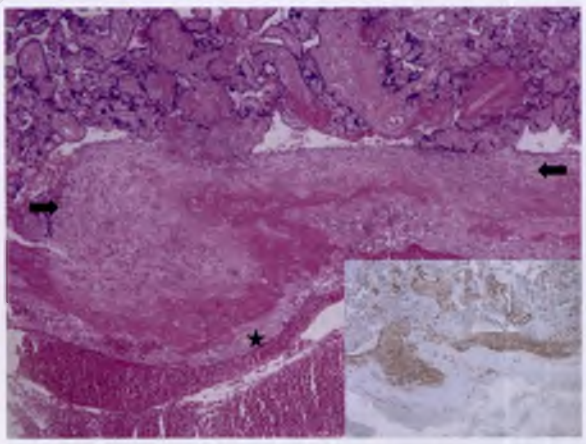

Figure 18.10 Low-power view of a basal plate plaque coating the intervillous aspect of a basal plate region (at the level of the arrows). The lesion appears pale with, in this case, a layer of eosinophilic fibrin(oid) separating it from the underlying decidua (star). The inset image is the corresponding area stained with smooth muscle actin, which highlights the myofibroblasts within the lesion. Image provided with permission by S.M. Jacques, Hutzel Women's Hospital, Detroit Medical Center, Detroit, MI.

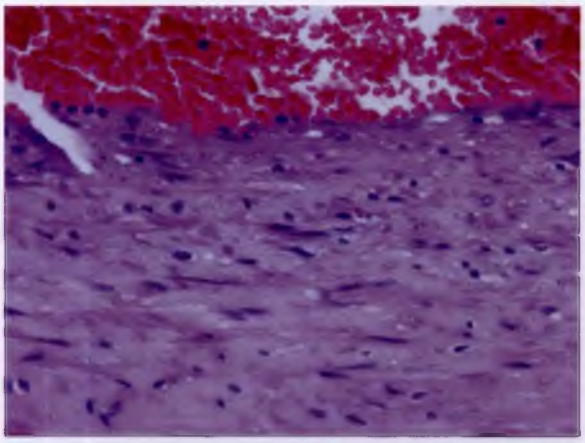

Figure 18.11 The spindle cells within basal plate plaques are arranged parallel to the basal plate surface and are distributed in a myxoid-appearing stroma. Occasional scattered lymphocytes are often present.

Clinical Context: The clinical significance of the basal plate plaque has not been definitively established, as there has only been a single descriptive study of these lesions to date, and there have been no prospective analyses focusing on their clinical features. Most small examples are likely to be insignificant. Larger examples have only been seen by the authors in placentas showing other pathology, e.g., distal villous hypoplasia; therefore these larger plaques may be secondary findings in placentas with other primary and more clinically significant pathology.

Proposed Pathogenesis: Blood and fibrin may be deposited in areas of stagnation or turbulence on the intervillous space side of the basal plate in a manner analogous to the formation of subchorionic intervillous thrombi beneath the chorionic plate. In contrast to subchorionic lesions and other parenchymal thrombi, organization of the thrombus occurs through ingrowth of myofibroblasts that appear to be maternal in origin. It is likely therefore that the proximity to maternal cells in the basal plate allows thrombus organization to occur. Small lesions appear to form at sites where turbulence or stasis may be expected to occur in a normal placenta, such as small depressions in the basal plate or in the angle between anchoring villi and basal plate. Such lesions are fairly common. Larger lesions that may bridge between anchoring villi may reflect more significant abnormalities of flow in the intervillous space; they may therefore be markers of more global placental pathology.

Gross Features: As there is significant variability in the normal thickness of the basal plate, basal plate plaques which are generally small and less than 1 to 2 mm in thickness and are not generally visible grossly. Larger examples may however be visible as areas of discoloration and thickening along the basal plate.

Microscopic Features: The common forms of basal plate plaque are small and often inconspicuous lesions that appear to fill depressions in the intervillous space aspect of the basal plate. Most commonly the lesions are only 1–2 mm in size. Sometimes they form in the angle adjacent to anchoring villi. Initially composed of fibrin or fibrin and erythrocytes, the plaque forms when this is infiltrated by myofibroblasts and becomes progressively organized. These myofibroblasts are smooth muscle actin positive. Occasionally the lesions contain scattered lymphocytes. In rare cases the lesion extends across the basal plate in a manner not obviously associated with basal plate depressions (Figure 18.10). In this manner, they may bridge the space between adjacent anchoring villi, or be present in multiple slides in the same case. A similar-looking process may also be observed in vascular spaces at the basal plate. This reinforces the impression that it is the position in relation to the basal plate that allows such fibrin/thrombus accumulations to organize, in contrast to thrombi in other areas of the placenta.

Differential Diagnosis: There is a normal variation in the amount of decidua present at the basal plate, and this commonly causes variation in basal plate thickness. Increased perivillous fibrin(oid) deposition on the intervillous space aspect of the basal plate may also cause thickening. This is relatively common in small amounts and is distinguished by the lack of the distinctive spindle cell population. In increased fibrin(oid) deposition there may be encased villi, embedded extravillous trophoblast or a background process such as a basal chronic villitis. If immunohistochemistry is performed, smooth muscle actin positivity may also be seen with adherent myometrial fibers in cases of placenta accreta. In this latter scenario the smooth muscle actin positive spindle cells are larger, eosinophilic and located on the maternal aspect of the basal plate.

Ancillary Diagnostic Testing: Generally not necessary. Immunostaining for smooth muscle actin may be used to highlight myofibroblasts within the lesion.

Prognostic Implications: It is likely that small lesions have no clinical impact or significance. Larger lesions have only been observed in placentas showing significant background pathology such as distal villous hypoplasia. It is this background pathology that is likely to carry the clinical significance. Its utility may be to highlight the possibility that there is a background of abnormal development, particularly where assessment of placental development may be difficult to interpret, e.g. when the placenta is fragmented, at early gestational ages or following periods of in utero retention after fetal demise.

Knowledge Gaps: Prospective studies are required to establish thresholds for what represents a clinically significant size or amount of basal plate plaque formation. The authors have observed subjectively prominent plaques in a number of situations including distal villous hypoplasia, delayed villous maturation and placental increta, but such potential associations have not been prospectively examined.

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Chapter 19

Meconium Effects

Theonia K. Boyd

Meconium Effects (Meconium-Associated Vascular Necrosis, Meconium Myonecrosis, Pigment- / Meconium-Laden Macrophages In Membranes, Pigment- / Meconium-Laden Macrophages In Chorionic Plate, Pigment- / Meconium-Laden Macrophages In Chorionic Vessel Wall, Reactive Amnion Hyperplasia)

Definition: Meconium represents the first-expelled fetal/neonatal stool. Placental effects include pigmented macrophages consistent with meconium present in amnion/chorion membrane stroma, membrane chorion epithelium, membrane decidua, chorionic plate, and umbilical cord stroma; with or without associated fetal vasculitis, meconium myonecrosis, etc. Formatting in the diagnostic report is strongly encouraged with clinicopathologic separation into a tiered grading system (concept courtesy R. Redline, see Table 19.1).

Clinical Context: Ante- and intrapartum meconium discharge is identified in up to 12.0 percent of all low risk[1] and in 18.1 percent of all term pregnancies[2]. It is less common in the preterm period and is rare prior to 28 weeks' gestation. When antenatal meconium discharge is present in preterm fetuses, it has been associated with amniotic fluid infection and fetal vascular malperfusion[3]. The frequency, regardless of gestational age, is increased in clinical circumstances of intrauterine stress, as is the frequency of moderate to thick meconium, particularly with untoward fetal/neonatal outcome[2,4].

Proposed Pathogenesis: Opinions regarding the pathogenesis and clinical significance of antenatal meconium discharge are divergent. Some consider small amounts of meconium discharge in the last few weeks of pregnancy "physiologic," particularly with post-term fetuses[5–7], though scientific data for this contention in humans is lacking. Others consider all meconium passage as abnormal, even if due to presumptive intrapartum physiologic stressors rather than pathologic antenatal circumstances per se[7,8]. This author has adopted latter position. Regardless, thick or prolonged meconium discharge is associated with and therefore presumably incited by fetal distress[9,10]. See further discussion on this point ("Prognostic Implications" section) below.

Gross Features: Meconium passed very shortly before delivery does not have time to be deposited on or taken up within the extraplacental membranes or chorionic plate. Meconium that does discolor the placenta imparts a dark green hue when relatively fresh (Figure 19.1). As the interval between meconium passage and delivery lengthens, meconium discoloration transitions to shades including dusky brown and with admixed hues of red or yellow (Figure 19.2). After several hours, the umbilical cord can also become meconium-discolored, changing likewise as the discharge-to-delivery interval increases from green to mixtures of brown-red-yellow (Figure 19.2). Meconium-stained tissues are typically opaque and diffluent (slimy); amnion separation is common in this setting.

Microscopic Features: Meconium passed recently with respect to delivery can be seen as particulate orange-brown amorphous deposits on the membranes and/or chorionic plate. It is most likely to be identified between layers of the membrane roll, admixed with other particulate material such as red cells and fetal squamous cells (Figures 19.3 and 19.4). Meconium taken up within stromal macrophages initially appears orange-brown and globular, like its particulate counterpart (Figure 19.5). As time passes, meconium macrophage

Table 19.1 Gross and microscopic meconium features and associated clinical risk

Low grade/recent meconium exposure (roughly minutes to <3 hours prior to delivery)
Gross: No membrane or chorionic plate discoloration to faint (light green) meconium staining
Microscopic: Reactive amnion +/- amniocyte necrosis, membrane edema, particulate meconium without macrophages or pigmented macrophages in superficial membrane stroma
Clinical: Recent or thin meconium with respect to delivery; no meconium sequelae
Intermediate meconium exposure (roughly >3 to < 6 hours prior to delivery)
Gross: Green membranes and chorionic plate, diffluent (slimy) texture
Microscopic: Reactive amnion +/- amniocyte necrosis, membrane edema, meconium macrophages in membrane chorion and decidua and mid-deep chorionic plate stroma; +/- early umbilical and/or chorionic fetal vasculitis
Clinical: Meconium discharge hours prior to delivery, or moderate-thick (sequestered) meconium identified at delivery; increased likelihood of oropharyngeal meconium, increased risk of meconium aspiration
Prolonged meconium exposure (roughly > 6 to < 12 hours prior to delivery)
Gross: Dark green to admixed red/brown/yellow membranes, chorionic plate and umbilical cord, diffluent (slimy) texture
Microscopic: Dense meconium macrophages in decidua and deep chorionic plate connective tissue, meconium macrophages in outer-mid Wharton's jelly, umbilical and/or chorionic fetal vasculitis +/- early stages of acute chorioamnionitis
Clinical: Meconium stained neonate, hypoxia unrelieved by immediate delivery, meconium aspiration
Special consideration: Meconium associated vascular necrosis (meconium myonecrosis; > 12–16 hours prior to delivery)
Gross: As with prolonged meconium exposure; also with increased risk of umbilical ulceration and vascular rupture (see Chapter 16)
Microscopic: As with prolonged meconium exposure except meconium macrophages into deep umbilical and chorionic stroma, often abutting or within vascular walls; plus pyknotic and discohesive umbilical and/or chorionic myocytes polarized to periphery closest to amniotic fluid
Clinical: Meconium stained neonate, increased risk of catastrophic outcome including stillbirth and cerebral palsy/ permanent neurodisability

cytoplasm acquires a fainter orange-brown and bubbly or frothy appearance, likely due to meconium phagocytosis by cytoplasmic lysosomes (Figure 19.6). Meconium macrophages initially appear in the superficial amnion stroma of the membranes and chorionic plate (Figure 19.7). As time passes, meconium macrophages can be identified in ever deeper tissues layers: in the membranes, first the chorionic stroma, then the chorionic epithelium, and finally within the decidua (Figure 19.8); and in the chorionic plate, into progressively deeper layers of the stroma. Meconium uptake in Wharton's jelly is, relatively speaking, more difficult to detect (Figure 19.9), though the principle of superficial to deep migration with time holds true. As a separate consideration, the density of meconium macrophages along a horizontal plane in the membranes and/or chorionic plate is in general a reflection of meconium density within the amniotic fluid.

Associated findings: *Meconium myonecrosis*: As time passes between meconium discharge and delivery, the likelihood increases of meconium macrophages reaching the fetal vessels in the umbilical cord and/or chorionic plate. Meconium bile acids and phospholipases are toxic to myocytes, inducing a chemical myonecrosis mediated by a multitude of mechanisms that include inflammatory cytokine stimulation, complement activation, vasoconstriction and apoptosis[11–16]. Affected myocytes are those closest to the amniotic fluid, on the outer perimeter of umbilical vessels and/or toward the surface of the chorionic plate (Figure 19.10). Damaged myocytes appear rounded and discohesive, with variably discernible cytoplasmic hypereosinophilia but with clear nuclear pyknosis (Figure 19.11), with or without cellular dissolution as defined by loss of nuclear basophilia and/or fragmentation (Figure 19.12). Meconium

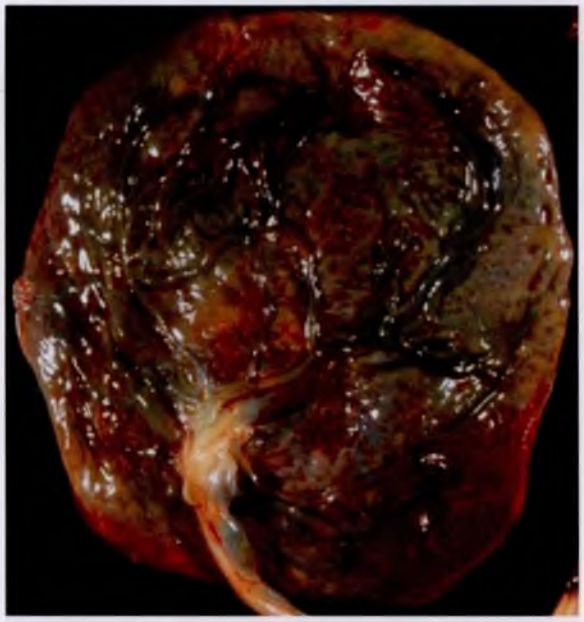

Figure 19.1 Recently passed meconium imparts a green hue to the fetal surface and extraplacental membranes (not shown), which remain fairly translucent but may feel diffluent upon palpation.

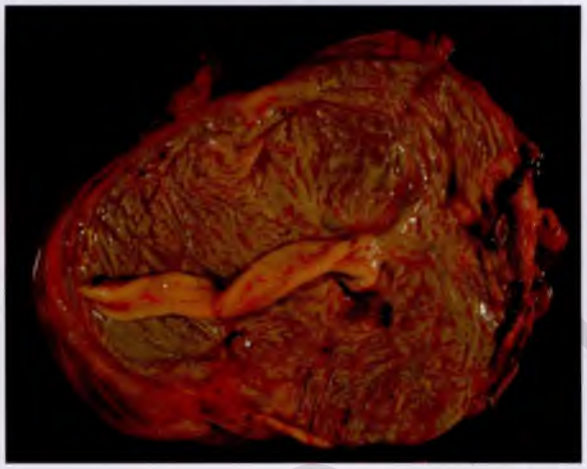

Figure 19.2 More remote meconium discharge, with green-brown discoloration of the fetal surface and extraplacental membranes (not shown), which are opaque; note similar umbilical cord discoloration and opacity.

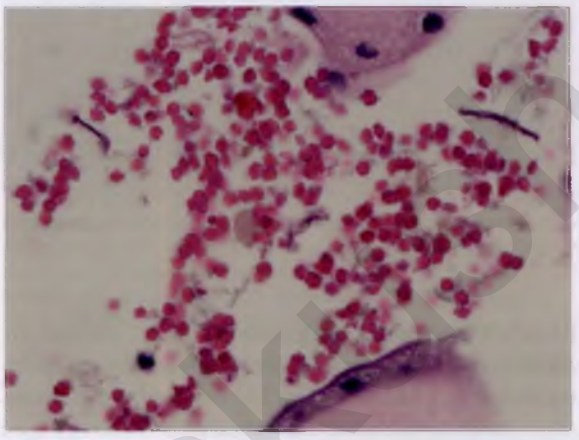

Figure 19.3 Particulate meconium (center and to right), which appears amorphous, orange-brown and globular, admixed with red cells and fetal squames.

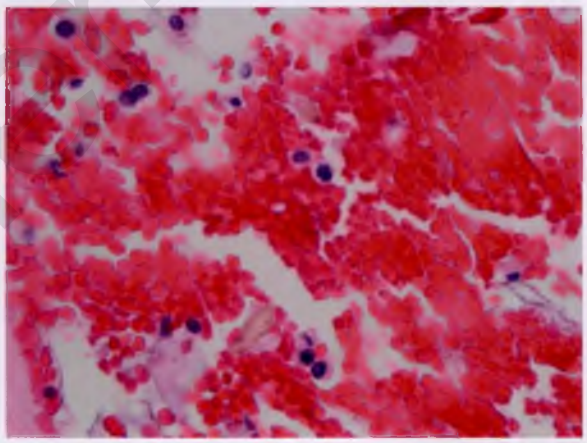

Figure 19.4 Particulate meconium (center top and bottom), which appears amorphous, orange-brown and globular, admixed with blood.

macrophages are frequently seen abutting or traveling into vessel walls. *Fetal vasculitis*, in this context a non-infectious chemotactic response to meconium[11–13] and/or mural damage, is not uncommonly seen in conjunction with placental meconium. Generally speaking, fetal vasculitis out of proportion to maternal inflammation is a commonly observed pattern in conjunction with meconium uptake into the umbilical cord and chorionic plate. *Reactive amnion hyperplasia*: a nonspecific response to local irritants, is frequently seen with meconium. In addition to morphologic changes, amniocyte meconium-staining and necrosis can also occur. Table 19.2 lists time frames for meconium-associated microscopic findings[17]. Although a few publications have differed with respect to time frames of meconium passage and placental uptake patterns, the cited table correlates most closely with this author's personal experience. *Normoblastemia*:

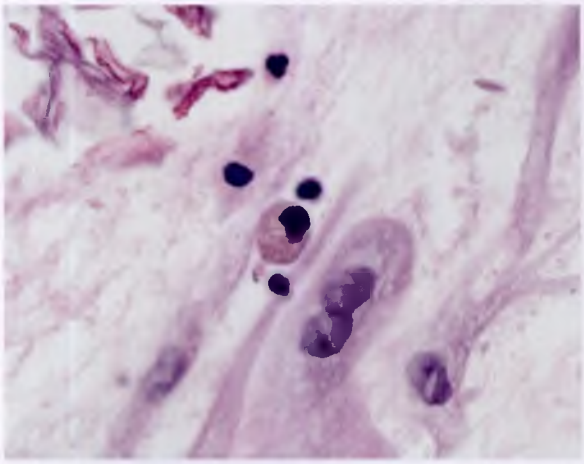

Figure 19.5 Superficial stromal meconium-laden macrophage (center), with grainy cytoplasmic uptake.

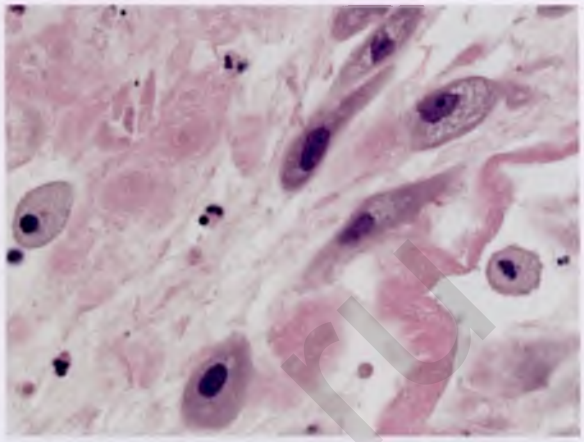

Figure 19.6 Decidual meconium-laden macrophages (2, 3 and 9 o'clock), with foamy and faintly brown-hued cytoplasm (higher magnification of Figure 19.8).

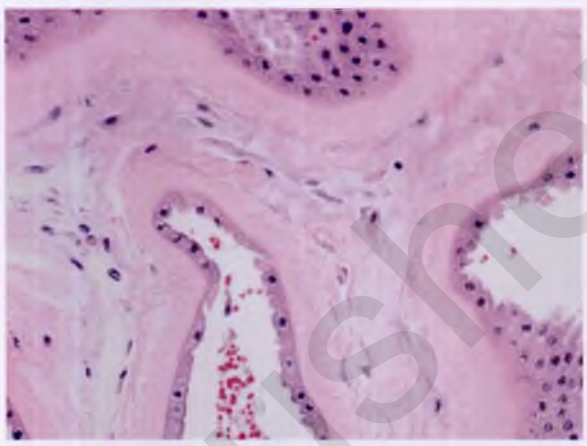

Figure 19.7 Superficial stromal meconium-laden macrophages, appearing orange-brown and in conjunction with clinically noted meconium passage.

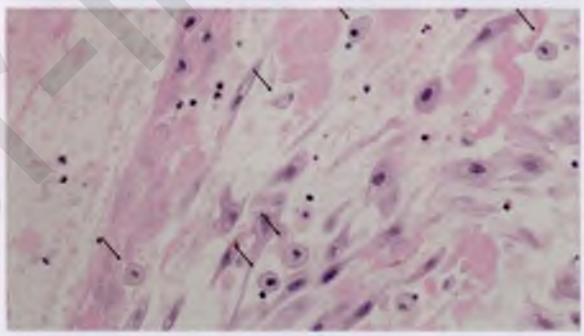

Figure 19.8 Decidual meconium-laden macrophages (arrows), with relatively inapparent light brown foamy cytoplasm (lower magnification of Figure 19.8).

Circulating nucleated red cells are typically present in meconium-stained placentas. They too, when increased, reflect an *in utero* response to fetal stress, as determined by the association among meconium, nucleated red cells, and non-reassuring fetal heart tracings[18]. See Chapter 20 for further details.

Placental pathology: In a general sense, intrauterine disorders associated with meconium discharge usually exhibit placental footprints – gross and/or histologic findings – that indicate operative mechanism(s) of intrauterine stress leading to antenatal meconium discharge[19,20].

Pitfalls/Differential Diagnosis: Grossly, meconium discoloration can be indistinguishable from chorioamnionitis. Microscopically, orange-brown hued pigmented membrane and chorionic macrophages include those due to hemosiderin and likely other pigment(s) (e.g., lipofuscin). Hemosiderin is identifiable by Prussian blue staining; other pigments including meconium lack specific identifying characteristics. A suggestion for accurate meconium identification is to require additional confirmatory evidence by way of clinically noted meconium, appropriately discolored membranes, or the microscopic detection of particulate meconium. Amnion necrosis alone is nonspecific and is therefore insufficient. The coexistence of chorioamnionitis can obscure detection of meconium uptake, in which case it is easiest to search for

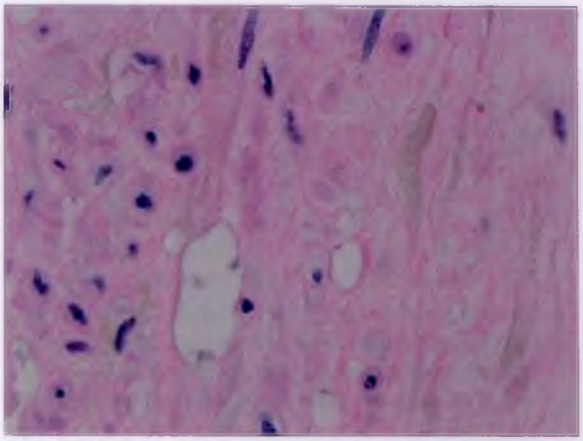

Figure 19.9 Meconium macrophage cytoplasm in Wharton's jelly; these cells are unusually evident in this location.

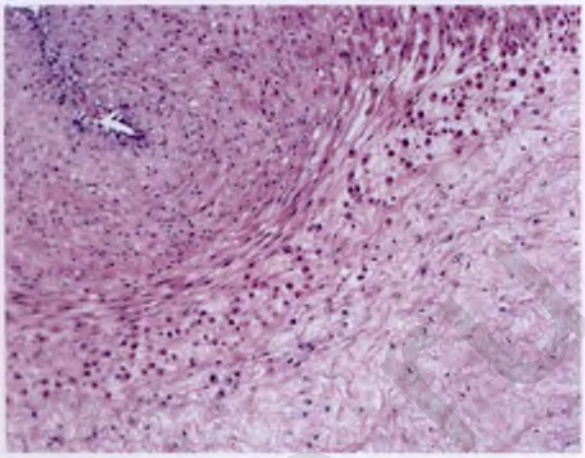

Figure 19.10 Meconium myonecrosis, with outer myocytes appearing hyperchromatic, rounded and discohesive; perimeter of umbilical cord on lower right. Image provided with permission by D.J. Roberts, Massachusetts General Hospital, Boston, MA.

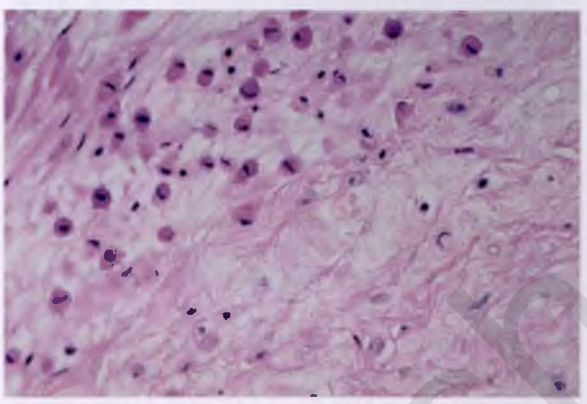

Figure 19.11 Meconium myonecrosis (higher magnification of Figure 19.10), with hyperchromatic, rounded and discohesive myocytes; relatively inapparent meconium macrophages are interspersed. Image provided with permission by D.J. Roberts, Massachusetts General Hospital, Boston, MA.

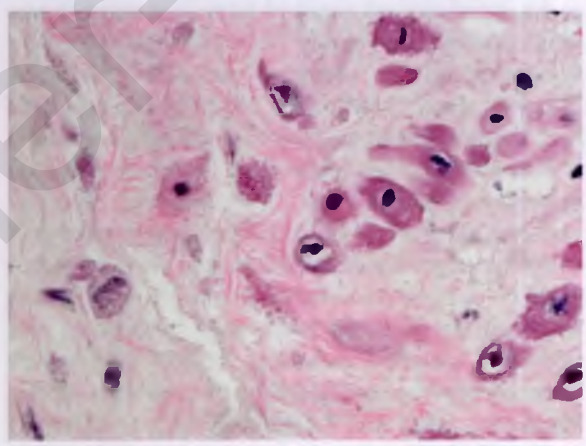

Figure 19.12 Meconium myonecrosis, with central myocyte cytolysis; meconium macrophages evident to left of myocytes. Image provided with permission by D.J. Roberts, Massachusetts General Hospital, Boston, MA.

meconium macrophages in areas of relatively less dense membrane and chorionic plate inflammation.

Ancillary Diagnostic Testing: There are no currently informative meconium-specific tests in the pathology laboratory. Clinically, neonatal chest imaging may be indicated to assess features of meconium aspiration. Neonatal meconium can be tested for antenatal maternal ingestion/inhalation/injection of noxious substances that cross the maternal-fetal blood barrier and are excreted in stool. Neonatal tests performed in the setting of antenatal meconium discharge range from general laboratory work such as complete blood counts, blood gases, and neonatal glucose levels, to more targeted tests such as blood cultures and CNS imaging.

Prognostic Implications: Based upon clinical studies correlating the quality of meconium discharge at delivery, neonatal presentation, and neonatal outcome, moderate to thick meconium is associated with lower Apgar scores, neonatal acidosis, meconium aspiration, early onset seizures, abnormal CNS imaging, permanent neurologic injury, and stillbirth[18–23]. Meconium

Table 19.2 Meconium discharge-to-delivery interval: Microscopic placental changes and their timing

Reactive amnion hyperplasia/necrosis: 1 hour
Meconium macrophages within the membrane amnion/chorion stroma: 1–3 hours
Meconium macrophages within membrane chorionic epithelium and/or decidua: > 3 hours
Meconium macrophages within umbilical stroma (Wharton's jelly): > 6 hours
Meconium vascular necrosis: > 12–16 hours

myonecrosis in particular is an ominous predictor of poor fetal/neonatal outcome[24–26]. Separately, there are clinical implications, including testing indications, targeted to whatever underlying intrauterine processes stimulate significant meconium discharge. Most of these processes, as previously mentioned, are reflected in placental pathology.

Knowledge Gaps: "Physiologic" meconium discharge in late gestation: is it real? There remains scant objective literature to assess this contention, which is of little clinically relevant significance in a given case, except perhaps pathologists' thresholds for diagnosing meconium macrophage pigment in placentas absent correlative evidence of antenatal meconium discharge. However, whether meconium can be physiologic does have implications in the medical malpractice arena.

Clinical literature exists with respect to placental meconium density and fetal/neonatal outcome. However, there are as yet no comprehensive retrospective placental studies of risk stratification with respect to fetal/neonatal outcome based on meconium density, estimated length of discharge prior to delivery, and associated placental pathology. In the interim, we strongly encourage consideration of meconium reporting in accordance with the proposed tiered system outlined in Table 19.1, for which there is partial literature support, but an abundance of authors' personal experiences. It is critical to underscore these are guidelines for which not every element will be present in a given case, and for which there is overlap, therefore it is suggested they be followed as a "best fit" construct.

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Chapter 20

Increased Circulating Fetal Nucleated Red Blood Cells

Theonia K. Boyd

Increased Nucleated Red Blood Cells (Normoblastemia, Erythroblastosis Fetalis If Chronic)

Definition: Increased circulating nucleated red blood cells (NRBCs) represent the appearance of inappropriate numbers of immature red cells in the fetal circulation in response to various stimuli after the first trimester of gestation.

Clinical Context: NRBCs are released in circumstances of hypoxia, intrauterine infection, and with prolonged maternal hyperglycemia[1–10]. Specific etiologic stressors can be of maternal, fetal, placental or exogenous origin; and within those groupings, can range from acute to chronic in evolution. See Table 20.1 for a schematic representation of etiologic mechanisms. Of course, specific causes can and often do involve effects on multiple "systems." For example, maternal diabetes can lead to fetal hypertrophic cardiomyopathy, resulting in fetal hypoxia through reduced cardiac output. Diabetes can also lead to fetal hyperglycemia and polycythemia[10], which in turn predispose to placental fetal vascular thrombosis (fetal vascular malperfusion). Thus, a mechanism of initial maternal origin can lead to secondary fetal as well as placental disorders that, *in toto*, contribute to the overall burden of antenatal hypoxic stress, resulting in normoblastemia at delivery.

Proposed Pathogenesis: Historical literature considered that elevated fetal NRBCs could only be seen as an end consequence of enhanced erythropoiesis, mediated by erythropoietin-induced erythroid expansion, and thus by analogy were only identified in conditions of chronic intrauterine hypoxic stress. More recent literature cites experimental and clinical evidence that erythropoietin-mediated NRBC release occurs several hours (4+) following an appropriate stimulus, from pre-formed stores in the fetal bone marrow and liver[11–14]. However, mediators in addition to erythropoietin have been shown to induce

Table 20.1 Formula for translation of relative NRBCs to absolute NRBCs

Formula		
X NRBCs (in the placenta or neonatal blood) / 100 WBCs (in the placenta or neonatal blood)	=	Y NRBCs/mm^3 (ml) (in neonatal blood) / Z WBCs/mm^3 (ml) (in neonatal blood)
Substitute values		
Example: X = 20; Z = 16.5 x 10^3		
20 NRBCs (in the placenta or neonatal blood) / 100 WBCs (in the placenta or neonatal blood)	=	Y NRBCs/mm^3 (ml) (in neonatal blood) / 16.5 x 10^3 WBCs/mm^3 (ml) (in neonatal blood)
Stepwise calculation		
1) X x Z = Y x 100 (from formula)		
2) 20 x (16.5 x 10^3) = Y x 100; also expressed as 20 x 16500 = Y x 100 (hereafter from substitute values)		
3) 20 x 165 = Y		
4) Y = 3300 NRBCs/mm^3, also expressed as 3.3 x 10^3 NRBCs/mm^3		

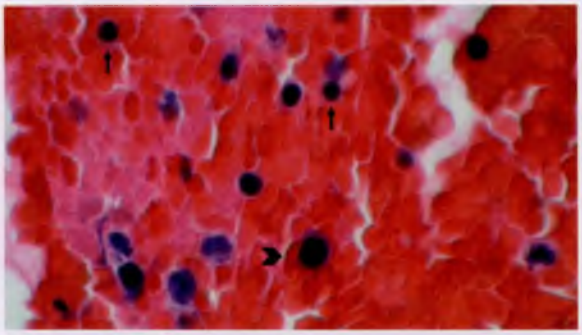

Figure 20.1 Umbilical blood normoblastemia. Orthochromatophilic erythroblasts (arrows), characterized by hyperchromatic round nuclei and cytoplasmic hue akin to anucleated erythrocytes. Polychromatophilic erythroblast (arrowhead), akin to its more mature orthochromatophilic counterpart but larger in size.

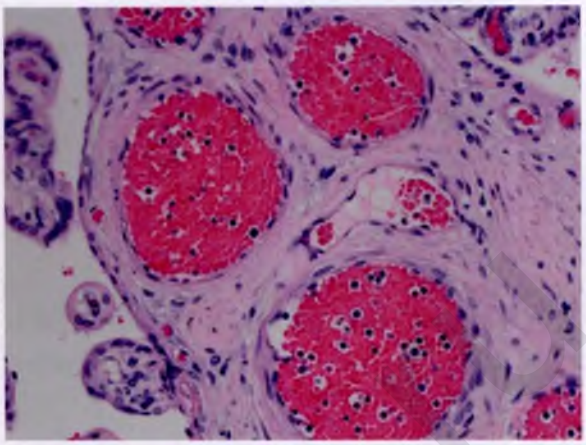

Figure 20.2 Stem vessel normoblastemia. Admixture of orthochromatophilic and polychromatophilic erythroblasts.

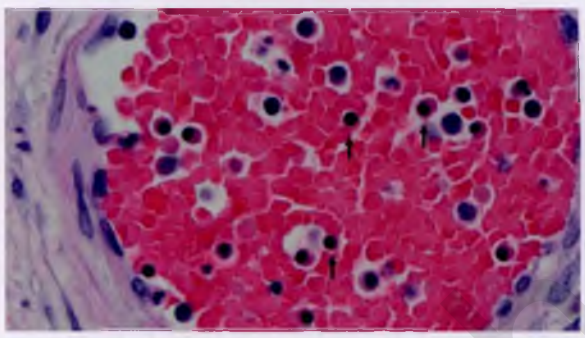

Figure 20.3 Stem vessel normoblastemia (higher magnification of Figure 20.2). Orthochromatophilic erythroblasts dominate this field (arrows).

NRBCs to enter into the peripheral circulation. In the setting of antenatal infection, elevated interleukin levels (e.g., IL-6) are associated with elevated NRBCs in neonatal umbilical blood prior to elevation in umbilical blood erythropoietin[15–17]. In addition to interleukins, *in vitro* research using human-derived cells and substrates has demonstrated the interaction between glucocorticoids and erythroid expansion[18]. In experimental animal models, antenatal administration of exogenous corticosteroids (e.g., dexamethasone) has also been associated with normoblastemia. Likewise, in animal models of experimentally induced intrauterine stress, elevated intrinsic fetal glucocorticoids (e.g., cortisol, corticosterone) have been demonstrated in conjunction with normoblastemia, suggesting an induction-release association[19,20]. Finally, fetal hyperglycemia secondary to prolonged maternal hyperglycemia can lead to elevated circulating fetal NRBCs[7,8]. In the rat, elevated serum glucose has been shown to mediate fetal erythropoietin secretion through direct activation of renal erythropoietin receptors[21]. In practice however, the interval between stimulus onset and the appearance of circulating fetal NRBCs is narrower than the literature reflects, particularly with respect to hypoxic modes of intrauterine stress. By virtue of this author's extensive personal experience, it takes about an hour after the onset of fetal hypoxia for the appearance of NRBCs into the fetal circulation. Conceptually, 1) the number of circulating normoblasts at delivery reflects both the intensity and duration of predisposing antenatal stimuli; and 2) the rate of neonatal NRBC decline following delivery roughly mirrors the time frame of antenatal rise.

Gross Features: None

Microscopic Features: Normoblasts, in their most mature form – orthochromatophilic erythroblasts, the ones initially released into the fetal circulation – appear as nucleated cells with hyperchromatic round nuclei and cytoplasmic hue akin to anucleate red blood cells (Figure 20.1). As the elapsed time between stimulus onset and delivery lengthens, more immature forms – polychromatophilic erythroblasts, with round larger nuclei having more open chromatin and somewhat more basophilic cytoplasm – are released into the peripheral circulation (Figures 20.1–20.3). It is not unusual to see binucleate (dyserythropoietic) cells with longer stress intervals; presumably, the stimulus for release takes precedence over culling

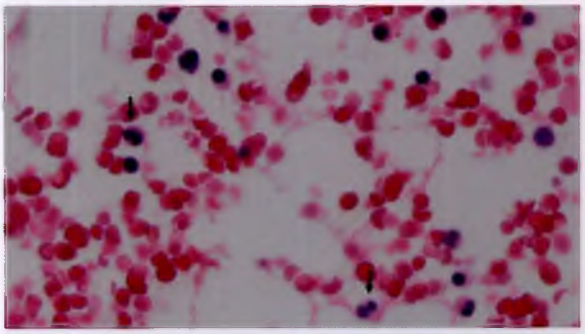

Figure 20.4 Fetal blood, placenta. Dyserythropoietic normoblasts, manifested as binucleate forms (arrows).

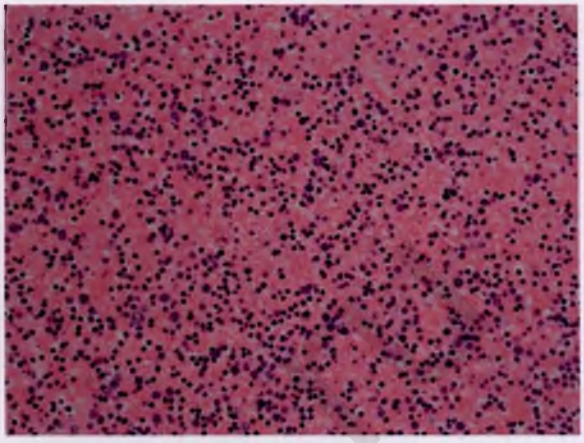

Figure 20.5 Fetal blood, placenta, with erythroblastosis fetalis. Virtually every nucleated cell is of erythroid lineage.

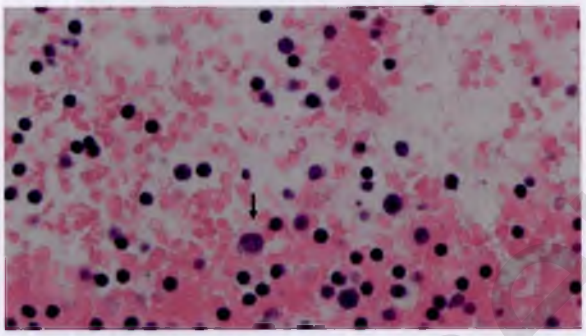

Figure 20.6 Fetal blood, placenta, with erythroblastosis fetalis (higher magnification of Figure 20.5). Erythroblast (arrow) with open chromatin, circular nucleus, and relatively basophilic hemoglobin-deficient cytoplasm.

abnormal cells prior to transit into the circulation (Figure 20.4). In circumstances of chronic ongoing stress with prolonged fetal survival, which is virtually always of hypoxic origin, such as Rh incompatibility, enhanced erythropoiesis and premature release of the most immature forms results in classic erythroblastosis fetalis (Figures 20.5 and 20.6). NRBCs present in the fetal circulation of the placenta are expressed as a ratio: the number of nucleated red cells is reported as a number relative to 100 white blood cells. With neonatal survival, this semi-quantitative value can be compared to early neonatal blood results for accuracy, with caveats. Factors that may influence comparison between placental and neonatal blood count may be affected by the following: 1) the interval between delivery and neonatal blood testing, particularly with continuing early postnatal stressors; and 2) ongoing early neonatal events that may influence the rate of neonatal NRBC decline. 3) Relative NRBCs may not accurately reflect the totality of fetal somatic registration of antenatal stress, since the relative NRBC value does not consider the fetal/neonatal white blood cell count (WBC). For a formula that corrects relative NRBCs to absolute NRBCs, see Table 20.2.

With respect to assessing risk of untoward neonatal outcome, the comparative literature is scant, and the experimental literature virtually non-existent. Dichotomous separation into low and high risk strata with respect to placental/neonatal NRBCs levels have, in a few studies, defined threshold levels for relative and corrected NRBCs associated with untoward outcome[22–27] (Table 20.3). For further clinicopathologic discussion, see Prognostic Implications section below.

Pitfalls/Differential Diagnosis: Pitfalls in recognizing NRBCs lie primarily in misidentifying mature lymphocytes as normoblasts (orthochromatophilic erythroblasts), given that the size of both is similar (lymphocytes 7–10 microns, normoblasts 8–12 microns)[28]. The distinction can be made by virtue of the features that define normoblasts: hyperchromatic round nuclei with uniformly dense chromatin and cytoplasmic hue akin to anucleate red blood cells. The next more immature form, polychromatophilic erythroblasts (10–15 microns), are larger than both mature lymphocytes and normoblasts, and therefore not likely to be mistaken for lymphocytes. However, they might be misidentified as monocytes. Polychromatophilic erythroblast nuclei are also round, but the chromatin is more open and the cytoplasm more grey. Proerythroblasts, the most

Table 20.2 Select causes of antenatal normoblastemia

A. Maternal
   1) Hypoxia:
      a. Acute:
         i) Abruption
         ii) Hypotension (e.g., shock)
         iii) Anemia (e.g., antepartum hemorrhage)
         iv) Uterine hypertonicity (e.g., excessive oxytocin)
      b. Chronic:
         i) Hypertensive and autoimmune disorders leading to maternal vascular malperfusion
         ii) Erythrocyte alloimmunity (e.g., Rh incompatibility)
   2) Infection:
      a. Sepsis (absent fetal or intra-amniotic infection)
   3) Prolonged hyperglycemia:
      a. Poorly controlled diabetes mellitus

B. Fetal
   1) Hypoxia:
      a. Cardiac defects
   2) Infection:
      a. Congenital bacterial/fungal pneumonia, sepsis
      b. Congenital viremia

C. Placental
   1) Hypoxia:
      a. Acute:
         i) Intrapartum cord compression
         ii) Fetal maternal hemorrhage
      b. Chronic:
         i) Non-infectious chronic villitis
         ii) Massive perivillous fibrin/maternal floor infarction
         iii) Fetal vascular malperfusion
         iv) Mesenchymal dysplasia
   2) Infection:
      a. Intraplacental virus (e.g., CMV)
      b. Intraplacental bacteria (e.g., Listeria)
      c. Intraplacental parasite (e.g., Toxoplasma)

D. Exogenous
   1) Hypoxia:
      a. Maternal smoking
   2) Toxic:
      a. Maternal carbon dioxide toxicity

Table 20.3 Threshold values for NRBCs and increased risk of poor outcome in term neonates

Values	Reference
Expressed as relative NRBCs	
1. >24 NRBCs/100 WBCs	Ferber 2003; neonatal NRBCs and NRFHTs
2. 26^{+} NRBCs/100 WBCs	Phelan 2007; neonatal NRBCs and asphyxia
3. Mean 29.5 +/- 26 (range 7–144) NRBCs/100 WBCs	Goel 2013; cord NRBCs and perinatal asphyxia
4. >11 NRBCs/100 WBCs	Boskabadi 2016; NRBCs and perinatal asphyxia
Expressed as absolute NRBCs	
5. $2.5^{+} \times 10^{3}$ NRBCs/mm^3	Redline 2008; neonatal NRBCS and CP
6. 2050^{+} NRBCs/mm^3	Walsh 2013; neonatal NRBCs and encephalopathy

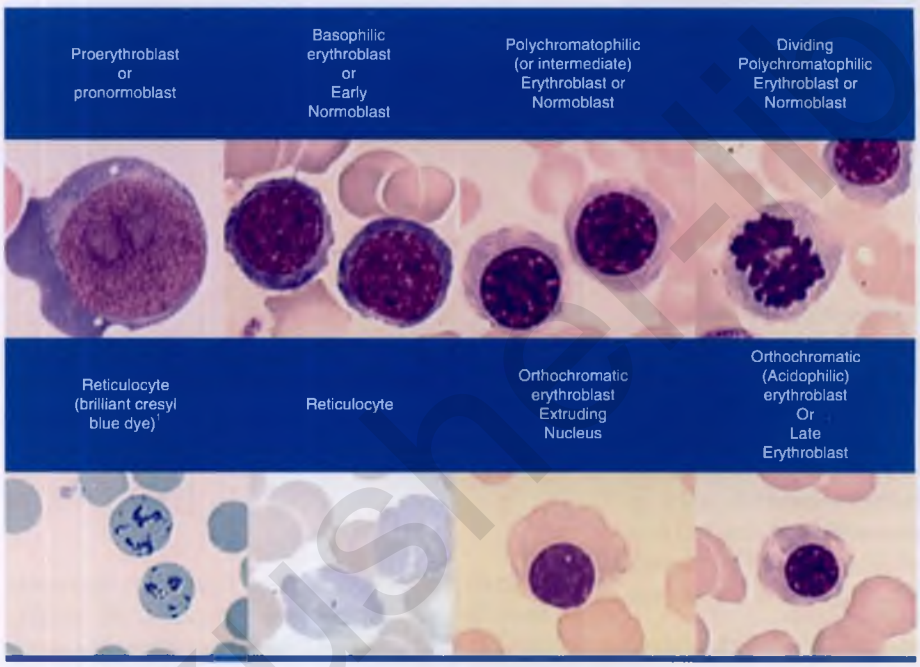

Figure 20.7 Erythroid precursor morphologies.
Source: www.slideshare.net/rtibloodinfo/all-about-blood-from-rtibloodinfo; slide 45.

immature of the erythroid lineage, are larger still (17–24 microns) with a high nuclear:cytoplasmic ratio, open chromatin with nucleoli, and basophilic cytoplasm. They may be mistaken for other hematopoietic precursors, particularly myeloblasts, monoblasts, or large lymphocytes. In the context of overt normoblastemia however, proerythroblasts should be recognized as members of their more mature erythroid counterparts. See Figure 20.7 for a comparison of erythroid precursors.

Associated Clinical and Pathologic Findings: *Mild normoblastemia* is associated with circumstances of recent – typically hypoxic – stress with respect to delivery, including physiologic intrapartum stress and pathologic acute intrapartum events. Placental pathologies, if present, tend to be early/mild; or they reflect the early evolution of pathology associated with catastrophic events occurring shortly before delivery. Recently discharged or thin meconium and hyperglycemia may be present. If initial Apgar scores are low, they typically rebound unless the stressor is brief but catastrophic.

Moderate/severe normoblastemia is associated with non-acute placental pathology, a longer NRBC

postnatal clearance time, moderate to thick meconium, a greater risk of persistently low Apgar scores, fetal growth restriction, neonatal acidosis, neonatal seizures, hypoglycemia and thrombocytopenia. There is an increased risk of permanent untoward outcome, most specifically neurodisability in live births, and of stillbirth[3,16,26,27,29–37].

Ancillary Diagnostic Testing: If infectious, considerations include maternal, fetal/neonatal and/or placental cultures, serology, and molecular tests for specific organisms. If hypoxia/asphyxia related, indicated tests include neonatal CBC, CNS imaging, and serum glucose levels; maternal evaluation could include Kleihauer-Betke testing.

Prognostic Implications: With prominently elevated NRBCs, associated conditions with an increased risk of untoward outcome in live births include sepsis, neonatal seizures, neurodisability, multi-organ dysfunction, and neonatal death. In fetuses, there is an increased risk of stillbirth. These conditions are usually associated with non-acute intrauterine processes that leave tell-tale placental findings (pathologic "footprints")[3,16,26,27,29–37].

Knowledge Gaps: The literature is varied with respect to assessing normative NRBC values by gestational age[38–45]. The reasons are multifactorial, and include the following considerations: 1) all preterm births are abnormal, in so far as they occur, whether spontaneously or induced for maternal and/or fetal indications, prior to term; 2) term neonates with normal deliveries do not typically have CBCs drawn or placentas submitted for pathologic evaluation; and 3) due to the absence of CBC data, rates of post-delivery NRBC decline in the neonatal circulation are under-reported. Thus, comparison of NRBC values at delivery; placental pathologies that include assessment of severity and chronicity; rate of neonatal NRBC clearance; and serial neonatal NRBC testing have yet to be systematically addressed. Future clinico-pathologic studies that focus on risk stratification based on a multitude of NRBC factors with respect to fetal/neonatal outcome could include: simultaneous consideration of relative and absolute numbers, erythroid precursor maturity in fetal/neonatal blood, and postnatal clearance times.

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Chapter 21

Early and Late Membrane / Amnion Rupture and Amnion Nodosum

Suzanne M. Jacques and Faisal Qureshi

Amnionic Band Syndrome / Early Amnion Rupture (Other Names: Early Amnion Rupture Sequence (EARS); Amnionic Deformity, Adhesion, Mutilation (ADAM) Complex; Chorioamnionic Rupture Sequence; Amnionic Adhesion Malformation Sequence; Amnionic Band Disruption Complex; Amnionic Rupture Sequence; Constriction Rings; Streeter Dysplasia or Streeter Bands; Aberrant Tissue Bands; Congenital Annular Bands or Constrictions; Congenital Transverse Defects; Congenital Band Syndrome; Congenital Annular Defects)

Definition: Bands of amnionic epithelial-lined connective tissue extending from the fetal surface of the placenta, potentially encircling and amputating fetal extremities, encircling the cord with restriction of blood flow, or disrupting fetal organ development.

Clinical Context: *Amnionic band syndrome/early amnion rupture* (ABS) can be considered a composite of 3 patterns of abnormalities:

1. Placenta denuded of amnion with a thickened chorion
2. Fetal attachments or entanglements by fibrous bands or amniotic remnants
3. Fetal malformations, deformations, and/or disruptions which do not conform to any identifiable syndrome.

Fetal abnormalities associated with ABS can include abnormalities of the craniofacial region including anencephaly, exencephaly, and complex facial clefts; thoraco-abdominal wall defects including omphaloceles; and constriction bands with amputated extremities and digits. Some investigators consider the most characteristic findings of ABS to be "any fetus or infant with distal digital pseudosyndactyly, usually with deficiency of part of whole digit(s), with obligatory disruption of dermatoglyphic patterns" [1]. The type of abnormality can provide a clue to the timing of the amnionic rupture, with rupture in cases with severe abnormalities such as absent extremities, abdominal wall defects, and cleft lip occurring before 7 weeks of gestation, while an altered dermal ridge pattern and lack of a normal hair whorl occur closer to 16–18 weeks' gestation[2]. Early amnionic rupture has been reported in 1 of 56 previable aborted fetuses, with a male to female ratio of 1:1.2[3]. It is, however, much less frequent in later gestation, where it has been reported in 1 of 2,500 to 10,000 live births[4]. Most cases of ABS occur in chromosomally normal fetuses, although rare cases have been reported in association with trisomy 21 and trisomy 18[5].

Proposed Pathogenesis: Perhaps the most widely accepted hypothesis involves tear/rupture of the amnion with temporary loss of amniotic fluid, with fibrous bands forming between the chorion and mesodermal amnion, and with resultant entrapment of fetal parts[6]. Several other hypotheses regarding ABS have also been proposed, one of the earliest being the Streeter hypothesis, which suggests that amnionic bands and the associated limb defects arise early in gestation resulting from the same developmental disturbances, but that the bands are not the cause of the limb defects[7]. Still others have proposed that the defects are a result of impaired blood flow or "vascular steal," leading to disruption of various developmental processes; this

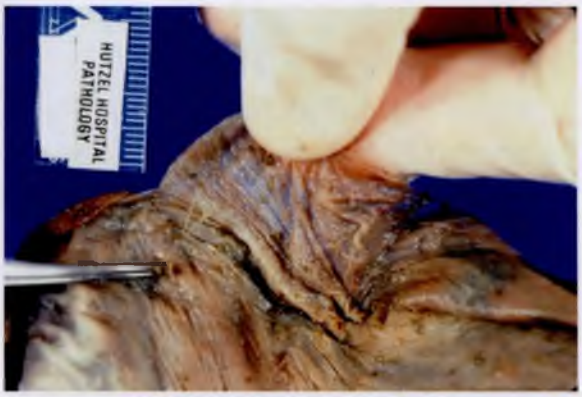

Figure 21.1 The amnion is detached, leaving the fetal surface with a dull, thickened, and opaque appearance. An amnionic band is attached to the fetal surface (held by forceps).

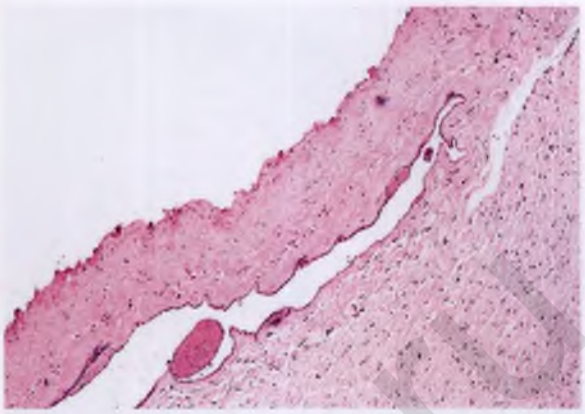

Figure 21.2 A delicate amnionic band composed of paucicellular connective tissue and covered by amnionic epithelium.

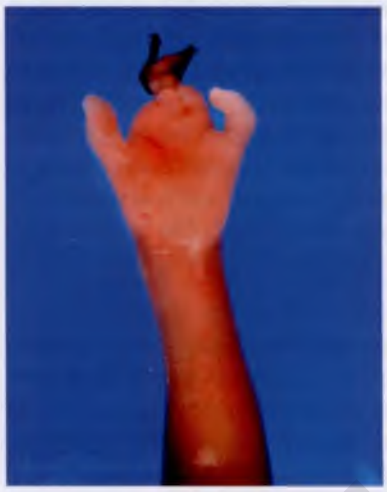

Figure 21.3 The fetal fingers are encircled and amputated by an amnionic band.

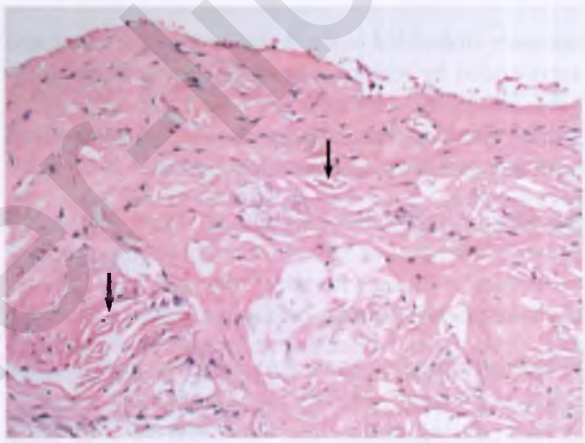

Figure 21.4 Amnionic bands: Anucleate squames (arrows) are embedded in fibrotic chorionic connective tissue, without an associated inflammatory response.

vascular steal supposedly occurs during weeks 4–6 of gestation[8,9].

Gross Features: The gross appearance of the placenta provides important clues to ABS. The fetal surface of the placenta is devoid of amnion, which may be present as a small, thickened fibrotic remnant attached to the cord insertion[10]. The fetal surface is thickened and opaque, and may have delicate bands or strands extending from it (Figure 21.1, 21.2). In occasional cases, the fibrous bands may actually encircle and constrict the umbilical cord, or encircle/attach to fetal limbs or other parts (Figure 21.3). Some placentas may show raised, irregular yellow-brown deposits on the fetal surface, which represent "vernix granulomata"[11].

Microscopic Features: The amnion is usually absent over part or most of the fetal surface, and is replaced by a single layer of attenuated cells, which represents nonspecific re-epithelialization and stains positively with pancytokeratin. Underlying the epithelium is thickened collagenous chorionic connective tissue. There may be a mild mononuclear inflammatory infiltrate, composed of lymphocytes and histiocytes in the connective tissue, but frequently there is no inflammatory response, and specifically there is no granulomatous inflammation. Occasional embedded anucleate squamous can also be identified in the thickened chorionic tissues (Figure 21.4). In some cases, so-called vernix granulomata are identified, composed of aggregates of anucleate and degenerated

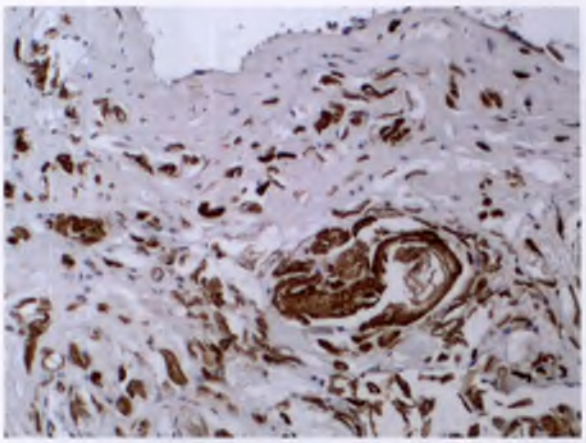

Figure 21.5 Amnionic bands: Immunohistochemical staining for pancytokeratin highlights the embedded anucleate squames.

squames embedded in the dense connective tissue and surrounded by scattered mononuclear inflammatory cells including lymphocytes and histiocytes[11]. Similar histologic changes are seen in placentas from both late gestation and previable fetuses[3].

Ancillary Diagnostic Testing: In cases where the squames are scant or difficult to identify, immunohistochemical staining with pancytokeratin helps delineate the embedded squames (Figure 21.5).

Prognostic Implications: An important aspect of the prenatal diagnosis of ABS is the possibility of intervention during pregnancy, especially for removing bands and preventing limb damage and improving fetal outcome[12]. It has been shown in animal model systems that the earlier limb repair surgery is performed in gestation, the better the morphologic and functional outcome[13]. ABS is sporadic, with no known genetic implications for future pregnancies. Only rare cases of apparent familial ABS have been described, and these familial cases may be coincidental[14]. Rare cases of ABS have been associated with amniocentesis; this may serve as an indication for caution in the use of amniocentesis in future pregnancies[15].

Knowledge Gaps: The events leading to the amnionic tear/rupture are not understood. Further understanding of the molecular biology of amnion rupture may clarify the pathogenesis of this entity.

Late Amnion Rupture / Amnion Chorion Dehiscence (Prolonged Amniotic Fluid Leakage, Subamnionic Dissection of Vernix Caseosa)

Definition: *Late amnion rupture/amnion chorion dehiscence* in late gestation can result in partial loss of the amnionic epithelium with embedded vernix squames in chorionic connective tissue or, if occurring very close to time of delivery, to dissection of vernix squames and lanugo hair between the amnion and chorion without embedded squames (subamnionic dissection of vernix caseosa).

Clinical Context: If the amnion chorion dehiscence occurs very close to the time of delivery, there is usually no associated history of oligohydramnios, prolonged rupture of membranes, significant maternal disease, or adverse neonatal outcomes, including prematurity or fetal abnormalities[16]. In contrast, in mothers with history of prolonged rupture of membranes and prolonged amnionic fluid leakage, associations include oligohydramnios and prematurity[17]. These infants may have "Potter-like" facies with limb contractures, and may be growth restricted (see below).

Proposed Pathogenesis: The pathogenesis of amnion chorion dehiscence is not known. The difference in the histologic patterns appears to likely be the result of the length of time elapsed between the membrane rupture and delivery. In subamnionic dissection of vernix caseosa, rupture of the amnion occurring close to the time of delivery, but before rupture of the chorion, may allow the amnionic fluid to dissect between the amnionic and chorionic layers, but without sufficient time for the vernix squames to embed in chorionic connective tissue[16]. In cases with prolonged amnionic fluid leakage, it has been suggested that separation of the membranes and decidua leads to amniotic fluid leakage, possibly due to amniocentesis, with leakage of fluid between the layers and with the embedded squames in the thickened chorion, suggesting a reparative phenomenon[17].

Gross Features: In subamnionic dissection of vernix caseosa, white flocculent or chalky-appearing deposits of vernix can sometimes be visualized beneath the

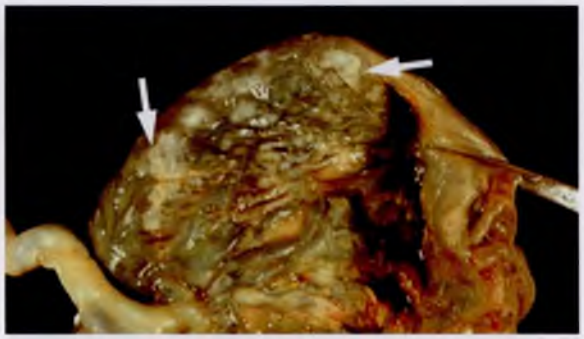

Figure 21.6 Subamnionic dissection of vernix caseosa: Aggregates of subamnionic flocculent white vernix (desquamated fetal squames and lanugo hair) can be seen grossly in some cases.

amnion (Figure 21.6). These deposits can be readily moved beneath the amnion with application of slight pressure. In occasional cases with extensive dissection of vernix caseosa, the membranes may have a diffuse milky appearance. Tears in the amnion have not been identified grossly, suggesting they are very small. In cases of prolonged amnionic fluid leakage no gross abnormalities have been described.

Microscopic Features: In subamnionic dissection of vernix caseosa, clusters of anucleate squames, and sometimes lanugo hair, are identified in the space between the chorion and amnion, in either the extraplacental membranes or the membranes of the chorionic plate (Figure 21.7). The deposits can be scant or diffuse, and there is generally no associated inflammatory response. Embedded squames in chorionic connective tissue are generally not seen, but if focally present, indicate that the rupture occurred at some time before the period immediately preceding delivery, allowing time for this reactive process to occur. In cases with history of prolonged amnionic fluid leakage, the amnion may appear normal, show coagulation necrosis, or be partially absent, and embedded squames are frequently identified within thickened chorionic connective tissue.

Ancillary Diagnostic Testing: Anucleate squames will be highlighted with immunohistochemical staining for pancytokeratin, although this is generally not necessary for diagnosis.

Knowledge Gaps: The pathogenesis of the amnion rupture is not understood. The limited number of cases reported to date hampers assessment of the frequency and possible clinical significance of these lesions.

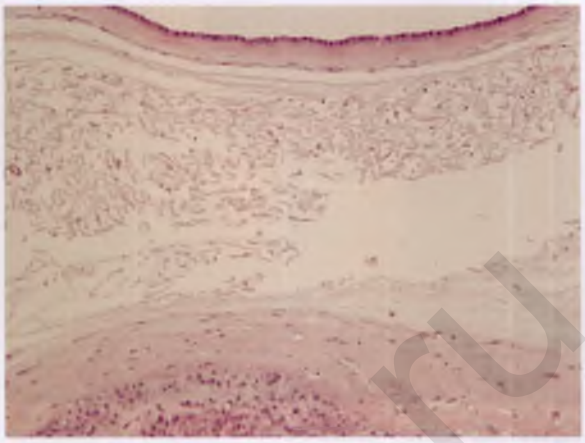

Figure 21.7 Subamnionic dissection of vernix caseosa: Anucleate squames are seen between the amnionic and chorionic connective tissue. No inflammation is present, and no embedded squames are seen in the connective tissue, consistent with a recent event.

Amnion Nodosum

Definition: Numerous small nodules adherent to but removable from the amnionic surface of the chorionic disc and extraplacental membranes, composed of granular debris with admixed vernix squames and lanugo hair.

Clinical Context: *Amnion nodosum* is an unusual finding, and is characteristically associated with severe and prolonged oligohydramnios[18–20]. As such, it is seen in fetuses with severe anomalies such as renal agenesis and sirenomelia leading to oligohydramnios through absence of fetal micturition[18–20]. It is also seen in other conditions associated with severe oligohydramnios, such as prolonged prelabor rupture of membranes and twin-twin transfusion syndrome (in the donor twin). It has a high risk of fetal and perinatal mortality, mainly because of lethal congenital malformations[21]. Amnion nodosum has also been reported in pregnancies without clinically diagnosed oligohydramnios, with reported associations including multiple gestations without twin-twin transfusion syndrome, maternal vascular malperfusion, and macerated stillbirth[21]. Amnion nodosum is seen in both the second and third trimesters[21].

Proposed Pathogenesis: The mechanism of formation of the nodules of amnion nodosum has been a subject of controversy. Hyperconcentration of the amnionic fluid might allow squames to adhere to the amnionic surface,

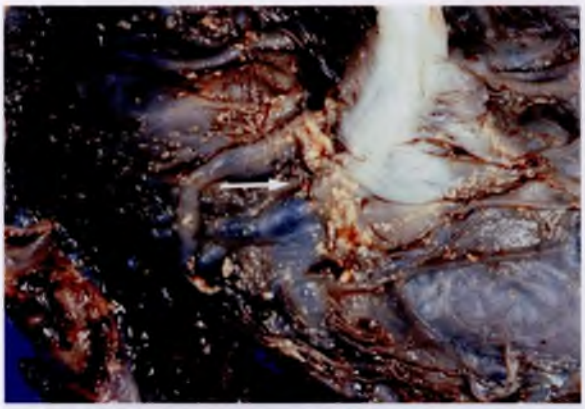

Figure 21.8 Amnion nodosum with the characteristic features of well-circumscribed, raised, granular-appearing yellow to tan nodules adherent to the fetal surface of the chorionic plate (arrow).

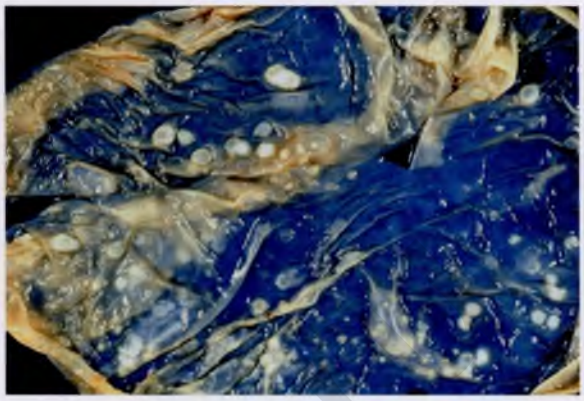

Figure 21.9 Squamous metaplasia with the characteristic small gray to white pearly plaques seen involving translucent extraplacental membranes (with blue background highlighting the plaques).

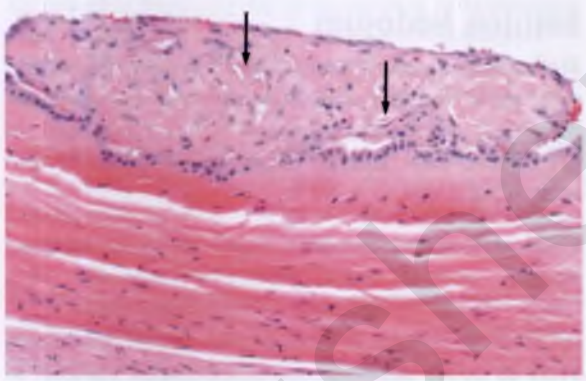

Figure 21.10 Microscopically, amnion nodosum appears as an irregular nodular accumulation of amorphous eosinophilic material with admixed vernix squames (arrows) and other debris. The nodule is adherent to amnionic epithelium.

producing secondary degeneration of the amnionic epithelium. Alternatively, oligohydramnios and fetal movement could lead to damage and death of the amnionic epithelium, resulting in a defect in the epithelium and allowing vernix to be deposited in a nodular fashion on the now-denuded surface[19].

Gross Features: Amnion nodosum appears as raised round to ovoid somewhat granular-appearing tan or yellow- brown nodules adherent to the amnion and usually measuring 1–5 mm in diameter (Figure 21.8). The nodules are typically seen on the surface of the chorionic plate and extraplacental membranes. Amnion nodosum must be distinguished from squamous metaplasia, which forms small gray to white pearly plaques, and is most commonly found in the area surrounding the cord insertion, but also found sometimes on the extraplacental membranes (Figure 21.9). Parenthetically, squamous metaplasia is a misnomer, as the amnion is a form of immature squamous epithelium continuous with the fetal skin. Amnion nodosum can be easily scraped from the amnion with a scalpel blade, while squamous metaplasia cannot, making this a simple method to distinguish between the two lesions at the grossing work station.

Microscopic Features: Amnion nodosum is an irregular nodular accumulation of eosinophilic debris with admixed vernix squames and hair (Figure 21.10). The nodule is attached to amnionic epithelium or to chorionic connective tissue, thus replacing amnionic epithelium. There is usually no associated acute or chronic inflammatory response to the lesions, or granulomatous reaction. Amnion nodosum is readily distinguishable from squamous metaplasia microscopically, the latter having an appearance identical to mature keratinized squamous epithelium of the epidermis (Figure 21.11).

Ancillary Diagnostic Testing: Immunohistochemical staining for pancytokeratin will highlight the squamous cells, but diagnosis can generally be made on H&E stained sections.

Prognostic Implications: When the amnion nodosum is seen in the context of prolonged severe

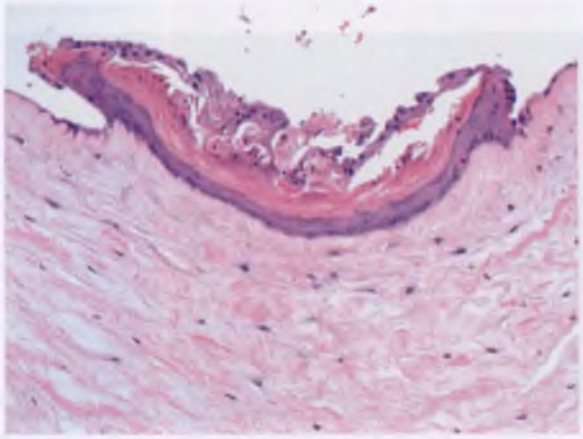

Figure 21.11 Squamous metaplasia is composed of mature keratinized squamous epithelium, histologically identical to that seen in the epidermis.

oligohydramnios, expected fetal associations include pulmonary hypoplasia and compression-associated malformations of the extremities and facies (Potter's sequence).

Knowledge Gaps: The pathogenesis of amnion nodosum remains incompletely understood.

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Chapter

22

Metastatic Tumors

Drucilla J. Roberts

Malignancies complicating pregnancy are rare, tragic situations thought to occur in about 1 per 1,000 pregnancies[1]. Metastatic malignancies to the placenta are even rarer, but the incidence is unknown, as placental examination is not universal. When metastasis occurs in the placenta, it can be from either a maternal or fetal primary, although maternal is much more common. Maternal malignancies metastatic to the placenta include solid and hematologic malignancies[2–4]. Among those from the fetus, neuroblastoma and hematologic malignancies predominate, but other rare tumors have been reported as well[5]. Transfer of the malignancy across the placenta has also been described from mother to fetus. Fetal metastasis to mother is controversial but theoretically can occur as well. It has been estimated that in those maternal malignancies that are metastatic to the placenta, 25 percent will spread to the fetus[4]. Those that metastasize to the fetus include, most commonly, melanoma, but also hematologic malignancies; breast, lung, gastric, adrenal, and gynecological cancers; and sarcomas[2–4]. Maternal solid malignancies metastatic to the placenta raise the cancer stage to level IV and portend a dismal prognosis. When maternal malignancies are vertically transmitted to the fetus, they have variable outcomes, some spontaneously remit while others progress rapidly to neonatal or pediatric death[4]. Fetal metastases to the placenta are evidence of widespread hematogenous dissemination, usually an advanced stage, and dismal prognosis.

Metastatic Malignancy (Maternal Primary)

Definition: Metastasis or involvement of the placenta by malignancy, including to any of the following locations: intervillous space, villous stroma, villous vascular spaces, and decidua.

Clinical Context: Usually, placental metastases from a maternal source occur in a pregnant woman with a known metastatic malignancy. Rarely is placental involvement the first sign of maternal malignancy. The most common malignancies that occur in pregnant women in order of prevalence are cervical cancer, breast cancer, hematological malignancies, and melanoma. Much less common are lung cancer, gastrointestinal carcinoma, other gynecological cancers, and sarcomas[2,6]. This order of prevalence is different that what is seen in placental metastases. By far, the most common malignancy metastatic to the placenta is melanoma[1,2,6], followed by hematologic malignancies, and then, much less commonly, breast and lung (see below)[2].

Proposed Pathogenesis: Hematologic spread of malignancy to the intervillous space with "attachment" of the malignancy to the trophoblast or to perivillous fibrin is the presumed method of maternal metastasis to the placenta. As the "metastasis" is typically only in the intervillous space (see "Microscopic Features" below) some prefer to describe these cases as "placental involvement" and suggest a sequestration-like phenomenon or a tumor embolism of sorts[5,7]. We believe that these are true metastases, as they are usually firmly adherent to the villi or villous stroma. As incidence during pregnancy and incidence of placental metastasis differ[2,3], there may be tropism for some malignancies (particularly melanoma) to the trophoblast[4] but this has not been rigorously studied. Although the true prevalence of metastatic involvement of the placenta is unknown, as placental examination is not routine, if published reports are at all representative, the approximately 100 reported cases as of 2008[2] suggest that the placenta is not a "ripe" organ for metastasis. Transplacental metastasis, from the mother through the placenta to the fetus, is rarer still[1].

Gross Features: Most placentas involved with metastasis, either from the mother or fetus, are grossly unremarkable. Occasionally maternal metastasis present with masses that can mimic infarcts (Figure 22.1a). We

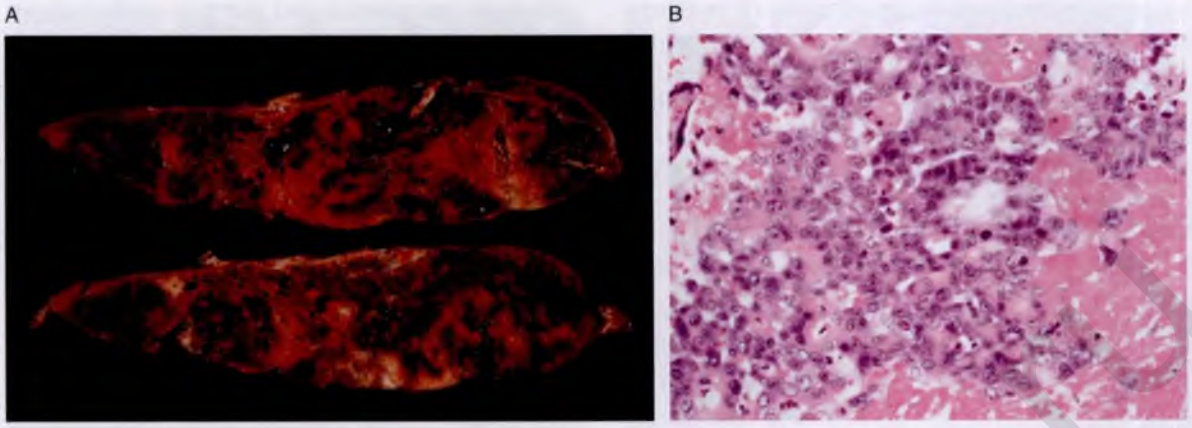

Figure 22.1 (a) Gross image of a placenta with multiple, variously sized parenchymal masses of metastatic maternal adenocarcinoma (courtesy of R. Redline). (b) Histology of a differenct case of metastatic colorectal carcinoma.

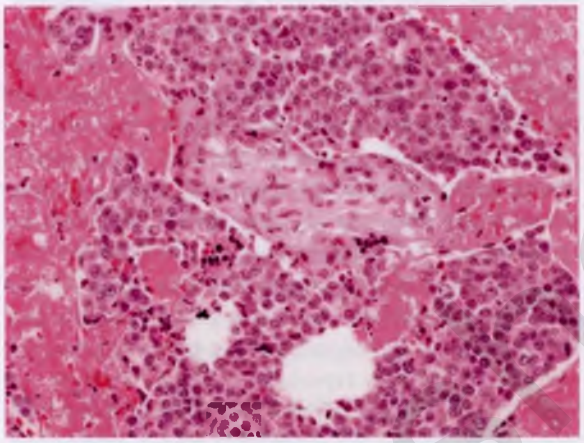

Figure 22.2 Metastatic maternal lung carcinoma in intervillous space surrounding but not invading the villus.

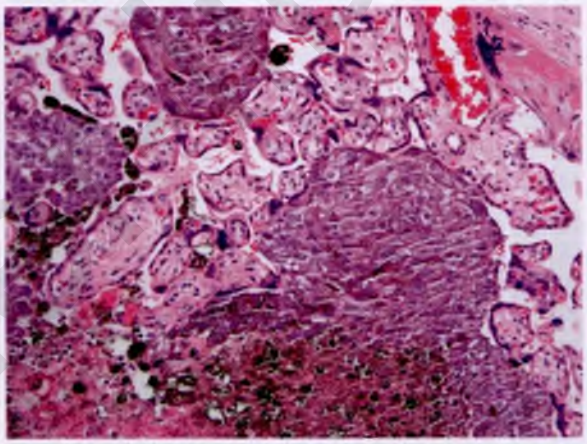

Figure 22.3 Metastatic maternal melanoma, pigmented.

have seen one case in consultation in which the placenta was sent for examination because it was grossly "lumpy," as noted by the clinician. Multiple foci of metastatic adenocarcinoma from a GI primary were present histologically (Figure 22.1b). The patient was not known to have a malignancy before the placental examination.

Microscopic Features: Tumor is usually present in the intervillous space surrounding the nearby villi (Figure 22.2). Sheets or clusters of malignant cells with features of their primary origin are haphazardly distributed throughout the placenta. Large tumor masses can be present, usually with abundant necrosis. Alternatively, the metastatic foci may be scarce, requiring multiple sections of the placenta to be examined. In one case. only 3 of 50 sections taken of the placenta demonstrated the metastases[8]. Invasion of the villous stroma increases the risk of transplacental metastasis to the fetus.

Selected Specific Maternal Metastatic Malignancies in Order of Reported Frequencies

Melanoma (Figures 22.3 and 22.4): Although melanoma is the fourth most common malignancy occurring during pregnancy[3], it is the most frequent malignancy to involve the placenta. This is in part due to its propensity for widespread hematogenous dissemination, but could also indicate a tropism for the placenta, as has been suggested by some[2,4,9].

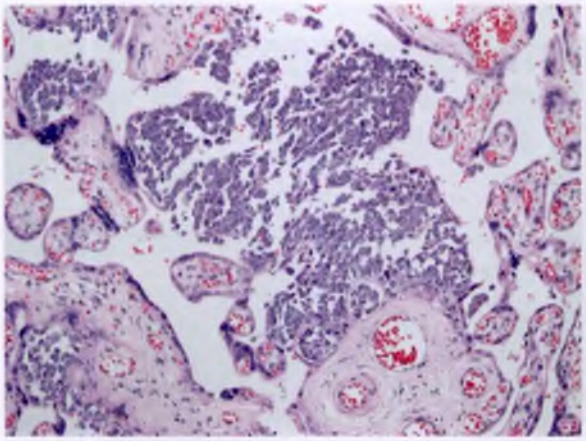

Figure 22.4 Metastatic maternal amelanotic melanoma.

Fifty-eight percent of all reported metastatic malignancies to the placenta are melanomas[2], and it's been estimated that if a woman has metastatic melanoma while pregnant, she has a 17 percent risk of seeding her placenta[2]. Melanoma is also the most common maternal metastatic malignancy to involve the fetus. Melanoma can present with macroscopic or exclusively microscopic lesions in the placenta, can be pigmented or amelanotic, and can be restricted to the intervillous space (Figure 22.4) or invade the villous stroma and fetal vasculature. Metastatic melanoma to the placenta has a high maternal mortality rate. Of the 28 reported cases to 2008[2] and in 2 more reports that we could find since[10,11], the maternal mortality rate was 100 percent within a few weeks or months of delivery; some deaths occurred within days. Although the fetal/neonatal transmission rate is low (8 reported cases from the 30 total placental metastases through 2016), the fetal/neonatal mortality rate is significant at more than 80 percent[2,10,11]. Survivors have been reported: one with spontaneous regression of the metastatic melanoma thought to be immunologically mediated[12,13]. Vertical transmission can take months to become evident[8], requiring active surveillance of all children born with metastatic melanoma to the placenta. Some factors that have been reported to predict unfavorable fetal/neonatal outcome include villous invasion, male sex, young maternal age (less than 30 years old), nodal metastases before pregnancy, more than 3 sites of maternal metastatic disease in the third trimester, and maternal death of disease within 1 month of delivery[8,14]. However, this has not been corroborated by others[9]. It has been suggested that all placentas from women with metastatic melanoma receive a full pathologic examination and that immunohistochemical stains be performed to identify isolated cells if metastases are not diagnosed by H&E alone[9]. It does not appear that pregnancy has an adverse effect on the course of melanoma in the mother[15], but risk of spread to the fetus with placental metastasis is high at 22 percent[16].

Hematological Malignancies: Leukemias and lymphomas are the second most common maternal malignancy to "involve" the placenta. They comprise about 15 percent of all maternal malignancies metastatic to gestational tissues[2]. In leukemias, "metastasis" is difficult to definitively diagnose, since if the maternal peripheral cell count is high there will always be malignant cells in the maternal space of the placenta. Sheets and clusters of blasts sequestered in the intervillous space have been considered a form of "metastatic" involvement[5,17]. Vertical transmission of the leukemia is rare but has been documented[18]. Although lymphomas during pregnancy are most commonly Hodgkin's disease, those involving the placenta are more commonly non-Hodgkin's lymphoma[2]. Transplacental fetal involvement can occur with placental lymphoma, usually aggressive non-Hodgkin's lymphoma[16,19,20]. Only one report of Hodgkin's lymphoma involving the placenta and fetus exists[21]. The maternal and fetal outcomes of placental involvement by hematological malignancies are typically grim, but survivors have been reported[22]. Pregnancy does not seem to have an effect on the course of the disease[16].

Breast Cancer: (See Figure 22.5.) Although breast cancer is the second most common malignancy complicating pregnancy, it is the third most common metastatic malignancy to the placenta, comprising 14 percent of all placental metastases[2]. Breast cancer is one of the few cancers whose prognosis may be affected by pregnancy, although the high maternal mortality of breast cancers during pregnancy may be mostly due to highly aggressive cancers at advanced stages of disease and not necessarily the pregnant state[16]. Metastatic spread to the placenta has been reported in 15 cases[2,23]; none spread to the fetus.

Lung Cancer: (See Figure 22.2.) Lung cancer is not common in pregnancy, but is the fourth most common malignancy to metastasize to the placenta, representing 13 percent of all such metastases[2]. Maternal outcome is dismal with a high mortality rate[24], although it is not clear if pregnancy alters the prognosis[25]. Placental

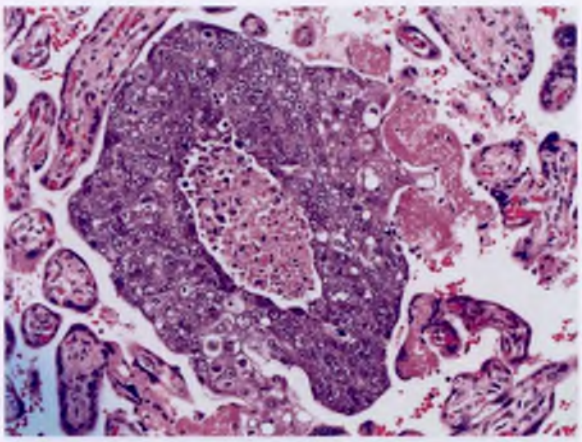

Figure 22.5 Metastatic maternal breast carcinoma.

and fetal involvement have been documented[16,25]. Although lung cancers presenting during pregnancy are equally divided between small cell and non-small cell types[26], most but not all gestational metastases from lung carcinoma are from small cell carcinoma[25,27,26,28,29]. Exceptional cases of lung carcinoma metastatic to the fetus have been reported, including both small cell carcinoma and non-small cell adenocarcinoma[27,29]. All affected infants have survived [16,27,29]. It is recommended that all placentas in women with lung cancer be evaluated pathologically, and if metastases are present, the infant should be screened for possible involvement[16].

Cervical Cancer: Cervical cancer is the most common malignancy during pregnancy, but is only rarely metastatic to the placenta. Rarity of metastatic involvement despite its frequency in pregnancy may be related to its typical lymphatic, rather than hematogenous, route of spread[2]. The usual early diagnosis and stage of cervical carcinoma due to surveillance may also make placental involvement exceptional. The 2 reports of cervical cancer involving the placenta were both metastatic tumors resulting in maternal death[30,31]. In one[30], the description of the cervical cancer stated it invaded the villous stroma, but fetal vascular invasion was not present. Neither infant had metastatic disease[30,31]. A third report suggests vertical transmission of a cervical neuroendocrine carcinoma, but placental pathology was not described[32]. In this case, fetal malignancy presented as bilateral temporal bone metastases, and the infant succumbed at the age of 40 months[32]. As vertical transmission has been described, all infants in cases with placental metastases should closely followed for metastatic disease.

Ancillary Testing: Immunohistochemical stains can help identify the origin of the malignancy if necessary, but in most cases the primary tumor is known with compatible histologic features in the placenta. Occasionally the source of the neonatal malignancy needs confirmation as being metastatic from the mother – in these cases fluorescent in situ hybridization (FISH) demonstrating an XX karyotype, can be useful if the neonate is male.

Prognostic Implications: Placental metastasis equates with stage IV disease in the mother, and the prognosis is grim with very high maternal mortality, often occurring shortly after delivery[2,8]. Preterm delivery is common, especially with metastatic melanoma[2]. Fetal/neonatal complications include those related to metastatic disease and often with associated prematurity. An interesting facet of metastatic disease to the fetus/neonate is the occasional occurrence of spontaneous remission, especially with melanoma (see above). Males are at highest risk for vertical transmission, have higher morbidity and mortality, and comprise approximately 75 percent of all reported congenital metastatic malignancies[2].

Knowledge Gaps: The apparently protective nature of the trophoblast against malignant invasion (rarity of placental metastasis compared to prevalence of malignancy during gestation) contrasts with the proposed tropism of melanoma for trophoblast; both findings remain understudied and poorly understood. Why metastatic disease is rare in the fetus also remains unexplained. Although an immune-related phenomenon has been suggested (i.e. that the fetus rejects the "foreign" malignant maternal cells), this is not supported by all of the data. Metastasis might be expected increase early in pregnancy before fetal immunocompetence, yet metastatic malignancies to the placenta or fetus are rare in early gestation. Why female infants are less likely than male infants to have metastatic disease[2] when one would expect males to be more likely to mount a response to female cells is unclear. Finally, histological evidence of immune response-related regression/rejection of tumor in either the placenta or the fetus/neonate is lacking[1].

Metastatic Malignancy (Fetal Primary)

Definition: Congenital malignancies with involvement of the placental fetal circulation or invasion into the chorionic villous stroma.

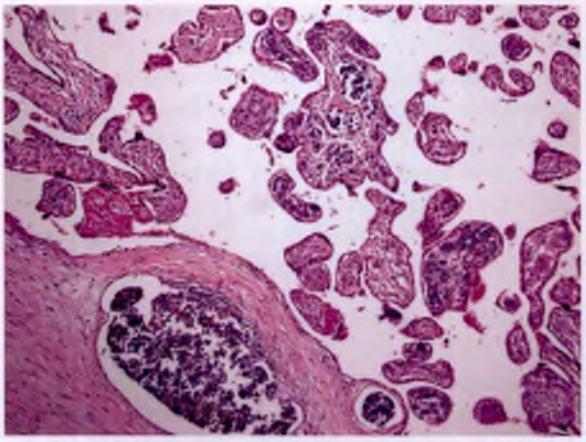

Figure 22.6 Fetal transient abnormal myelopoiesis (TAM) in a case of trisomy 21. Notice "blasts" clogging villous vessels.

Figure 22.7 Fetal B cell leukemia distending and "clogging" umbilical cord vessels. (Courtesy of C. Stefanovici).

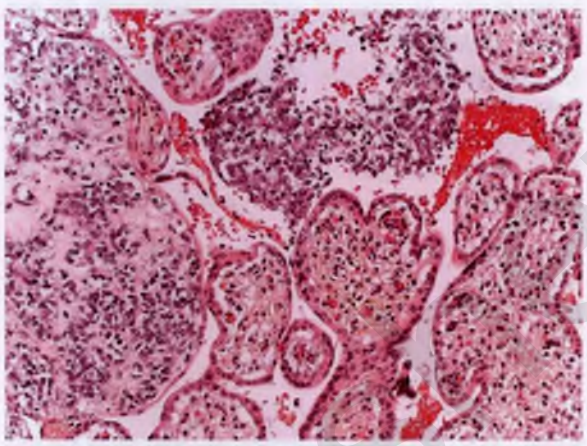

Figure 22.8 Fetal neuroblastoma "invading" maternal vascular space (courtesy of D. Bouronn Dal Soglio).

Clinical context: Fetal malignancies are extremely rare, and even rarer are disseminated fetal malignancies that involve the placenta. The most frequent fetal tumors involving the placenta are hematologic malignancies and neuroblastoma, but other tumors have been reported[5]. Often antenatal diagnostic testing has already identified a fetal mass (as in neuroblastoma cases) or hydrops fetalis (often a complication of hematologic malignancy). One unusual case described gestational origin of an EBV-associated lymphoma, apparently originating in the placenta without fetal or maternal tumor identified[33]. There are no characteristic maternal findings associated with fetal metastatic involvement of the placenta.

Proposed Pathogenesis: Hematogenous dissemination of congenital malignancy is usually associated with tumor in the villous vessels of the placenta. The malignant cells can be so numerous as to clog the small villous vessels, resulting in fetal and placental hydrops[5] (Figure 22.6). Rarely, these cells breach the vascular barrier to enter the villous stroma and, exceptionally, gain access to the maternal vascular space via invasion through the trophoblast[34–38].

Gross Features: Placentas with metastatic fetal malignancies are typically heavy, pale, and edematous[5]. Published cases have not reported grossly identifiable lesions, but we have seen one exceptional case in which the fetal vessels were grossly involved with tumor (Figure 22.7).

Microscopic Features: Malignant cells may be seen diffusely within small and large fetal vessels in the placenta. Often, the malignant cells cluster and clump in the villous capillaries, appearing to obstruct the lumen (Figure 22.6), a likely etiology for the often-accompanying hydrops placentalis and fetalis. Some reports describe villous invasion (malignant cells in the villous stroma outside of the vessel wall)[5], but this is rare. Several reports identified fetal malignant cells in the maternal vascular space of the placenta (illustrated in Figure 22.8)[25,34–37,39,40]. These rare cases signify invasion through the syncytiotrophoblastic barrier with "spillage" of the tumor into the intervillous (maternal) space. However, no maternal metastatic disease was identified in these cases.

Ancillary Testing: Immunohistochemistry can be used to phenotype the malignant cells. In addition,

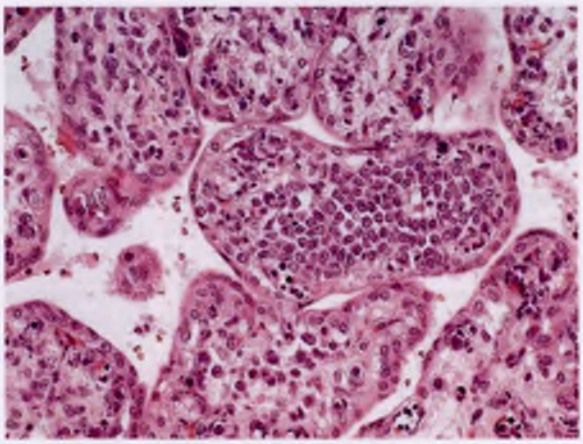

Figure 22.9 Fetal acute myelogenous leukemia "invading" villous stroma (courtesy of R. Redline).

FISH for the Y chromosome can be used to verify fetal origin of the tumor in cases of a male fetus[33,41].

Prognostic Implications: Placental involvement from a congenital malignancy is evidence of hematogenous dissemination and usually portends a poor prognosis for the fetus or newborn, with at least a 90 percent mortality rate[34]. Solid tissue malignancies metastatic to the placenta include most commonly neuroblastoma (16 cases reported to date[34,35]) Other fetal malignancies involving the placenta have been reported and include fetal renal rhabdoid tumor[42,43], melanoma[44], hepatoblastoma[45,46], rhabdomyosarcoma[40], undifferentiated sarcoma[39], and a primitive epithelial tumor[37]. True hematologic malignancies occurring in the fetus are generally lethal, either in utero or shortly after birth, perhaps due to a combination of liver failure, heart failure, and hypoxia. Congenital acute myelogenous leukemia (not associated with trisomy 21) has been reported with a high stillbirth rate[47–51]. Transient abnormal myelopoiesis (TAM)[52] seen in some cases of trisomy 21, can involve the placenta[34,36,53]. As TAMs usually spontaneously resolve within months[54], they aren't considered true malignancies. However, the histopathology of the placenta is dramatic and sometimes indistinguishable from a true acute myelogenous leukemia (latter pictured in Figure 22.9). In my experience, when TAM is present diffusely in the placenta and associated with hydrops placentalis and/or hydrops fetalis, the fetal/neonatal prognosis is grim. Maternal prognosis when there are fetal metastases to the placenta is good. Only one documented case of fetal-to-maternal metastatic spread has been reported: Nath et al.[41] described a case of a fetal primitive neuroectodermal tumor that spread to the maternal uterus. As the placenta was not examined and the fetal tumor was friable and disrupted at delivery, a transplacental route was not proven, and the metastatic focus could have resulted from direct seeding. Although the infant succumbed to the malignancy, the mother was reported well 2 years after tumor resection. Although transplacental transmission from fetus to mother has not been definitively documented, the presence of chorionic villous stromal invasion or tumor deposits in the maternal vascular space of the placenta is alarming and should be considered at least as a potential source of metastatic spread to the mother. Another maternal morbidity sometimes associated with fetal metastasis to the placenta is maternal edema accompanying fetal hydrops (so-called mirror syndrome)[35,55] (see Chapter 11).

Knowledge Gaps: The true prevalence of fetal metastasis to the placenta is unknown, as most placentas are not examined pathologically, but it appears to be rare. Unambiguous fetal to maternal transplacental transmission has not been reported, despite the presence of fetal malignant cells in the maternal vascular space[34–37]. How the malignant cells are cleared from this or other maternal tissues is unknown.

Congenital Nevus Cell "Metastases"

Definition: Involvement of chorionic villi by fetal nevus cells derived from *Giant Congenital Melanocytic Nevus* (GCMN).

Clinical Context: GCMN is a benign hamartomatous malformation of the skin defined as a nevus that is present at birth and predicted to reach at least 20 cm in diameter (for review, see Scalvenzi et al.[56] and Viana et al.[57]). The incidence is estimated to be from 1/1160 to 1/20,500 live births[58,59]. GCMN generally involves the trunk and may involve extremities. Placental involvement has been reported in rare cases[56,60–64]. As the differential diagnosis of GCMN includes malignant melanoma, placental involvement can suggest metastasis and confuse the true diagnosis.

Proposed Pathogenesis: Two theories exist to explain placental involvement by this benign process. One implicates a metastasis of sorts of the nevus cells to the placental villi, so-called benign metastasis[61]. The other, more commonly

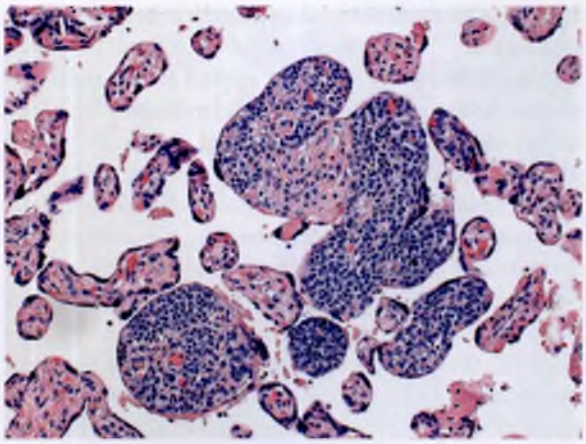

Figure 22.10 "Metastatic" nevus cells in villi: placental involvement associated with giant congenital melanocytic nevus (courtesy of S. Ravishankar and M. De Paepe).

accepted, is that the same process of abnormal neural crest cell migration and proliferation that produces the GCMN also results in aberrant nevus cells in the mesoderm of the chorionic villous[60]. Evidence for this theory includes the well-documented presence of nevi in other extra-epidermal sites (for review, see Sotelo-Avila et al.[62]). GCMN commonly have a gain of function mutation in NRAS at Q61[65,66]. This mutation in the embryonic neural crest cells is thought to drive them to proliferate and is likely instrumental in the phenotype of the lesion (for review, see Etchevers[67]).

Gross Features: Placental involvement by GCMN cells is usually not evident grossly. Only one case has been documented to have grossly identifiable pigmented nodules[62].

Microscopic Features: The nevus cells are present in the stroma of the stem and in the secondary and tertiary chorionic villi in nested aggregates (Figure 22.10). Involvement of maternal or fetal vascular spaces has not been reported. The cells are typical pigmented nevus cells: small, uniform blue cells with well-defined cytoplasmic borders. The nuclei are oval without prominent nucleoli. Mitoses are rare. Cytoplasmic pigment granules are present. Occasionally, pigment is also present in Hofbauer cells.

Ancillary Testing: The nevus cells are moderately positive for S100. Immunoreactivity for HMB45, Melan A, and MiTF has not been tested in GCMN, either at the primary site or foci of placental involvement. The pigment granules do not autofluoresce, are strongly positive by Masson stain, and can bleach after treatment with potassium permanganate. Molecular testing to identify the NRAS mutation has proven difficult in some cases[67].

Prognostic Implications: GCMC are considered benign, but there are many reports of malignant melanoma arising in patients with GCMN±. GCMN patients carry a 2–42 percent risk of transformation and a 6–14 percent lifetime risk of developing melanoma[58,69]. A small proportion of prepubertal patients (1–2 percent) with GCMN develop melanoma, a very high incidence for the general population of children[67]. There is no apparent increased risk of developing malignant melanoma when GCMN involves the placenta.

Knowledge Gaps: Although the biology of the primary GCMN has been well described, the mechanism of placental involvement remains poorly understood.

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Chapter

23

Heterotopias and Germ Cell Tumors

Suzanne M. Jacques and Faisal Qureshi

Hepatic Heterotopia (Hepatic Adenoma, Hepatocellular Adenoma, Hepatocellular Adenoma-Like Lesion, Benign Hepatocellular Tumor, Placental Hepatic Nodule)

Definition: Hepatic heterotopias are well-circumscribed nodules of benign fetal-type liver found in placental tissue.

Clinical Context: These rare placental lesions are single and are discovered incidentally. They can be less than 0.1 cm, or can be visible grossly, but are usually less than 1.5 cm[1–4]. Most have been described in preterm third trimester placentas or early term placentas[2–5]; however, microscopic lesions less than 0.1 cm have been identified in two second trimester placentas and one first trimester hydropic abortus[1]. One hepatic adenoma was described in a third trimester twin placenta, in association with a chorangioma[4]. No consistent clinical maternal features or adverse fetal outcomes are reported. Their frequency may be considerably higher than reported due to sampling, since they are often incidental findings on microscopic examination.

Proposed Pathogenesis: The histology, immunohistochemistry, and ultrastructural findings are compatible with embryonic liver tissue of 6–8 weeks developmental age[3]. Although frequently termed "adenomas" or "adenoma-like" because of histologic features resembling those of an adult hepatic adenoma, including the absence of portal tracts[2,5], the histogenesis of these hepatic nodules remains uncertain. It has been suggested that they represent a specialized monodermal teratoma, expressing pure endodermal differentiation[5]. Others have challenged the assessment that these hepatic nodules represent true neoplasms or teratomas, noting that reported teratomas typically occur between the chorion and amnion, while these can occur in the villous parenchyma[3]. Consideration of these lesions as heterotopias also may be imprecise because of the absence of portal vascular and biliary structures, but they may represent an ectopia or heterotopia of incompletely developed or embryonic hepatic tissue[3]. It has also been suggested that these hepatic nodules develop from displaced yolk sac elements with hepatocytic differentiation during early embryogenesis, making them rare examples of placental choristomas[2].

Gross Features: The cut surfaces of these well-circumscribed nodules are mottled tan-white to homogeneous dark red without necrosis or hemorrhage. The macroscopic lesions have been subchorionic, and most are less than 1.5 cm[2,3], but they have been reported as large as 7 cm in diameter[5].

Microscopic Features: These discrete, well-circumscribed nodules can be subchorionic or within stem villi, surrounded by a rim of fibrin and villous tissue[1,2]. The cytologic features resemble fetal liver, with cords and nests of polygonal epithelial cells with eosinophilic granular cytoplasm; round, centrally located nuclei; sparse nucleoli; and absence of mitotic figures or significant cellular pleomorphism (Figures 23.1, 23.2). There are intervening endothelial-lined sinusoidal spaces, in which hematopoiesis is typically present. Vascular congestion and small hemorrhagic foci can be present. These nodules do not include portal areas, bile ducts, or central veins, and do not include bile pigment.

Ancillary Diagnostic Testing: Positive immunohistochemical staining for Hep-Par1, alpha-fetoprotein, alpha-1 antitrypsin, pancytokeratin, and carcinoembryonic antigen may be helpful in confirming hepatic tissue.

Prognostic Implications: These rare lesions are discovered incidentally. Although most reported cases are in preterm deliveries, and reported cases include multiple gestations, it is not clear that the hepatic

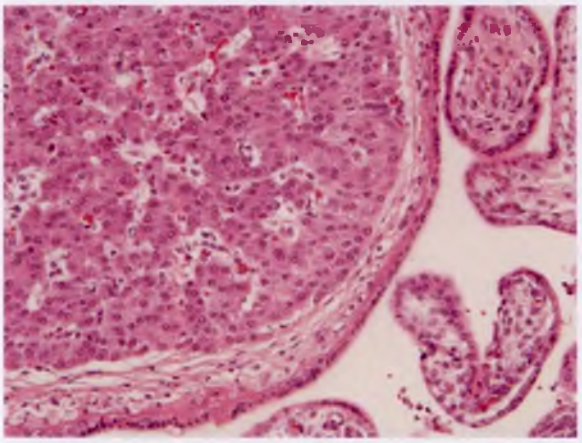

Figure 23.1 This villus contains a microscopic nodule of fetal-type hepatic cells, with features including cords and nests of polygonal epithelial cells with eosinophilic granular cytoplasm, and round centrally located nuclei.

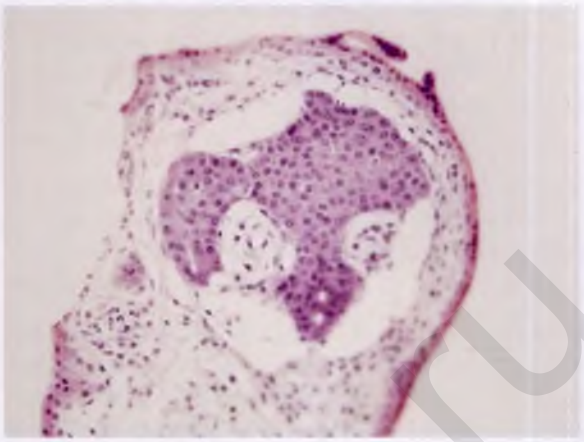

Figure 23.2 A minute nodule of hepatic cells is present within a villus in a first trimester hydropic abortus.

nodules are other than coincidental findings, or have any relationship with the pathogenesis of these conditions.

Knowledge Gaps: The embryogenesis of these lesions remains unclear, making their classification problematic. Although they are considered to be clinically insignificant, clearer understanding of possible clinical significance will require further study.

Adrenocortical Heterotopia (Adrenocortical Placental Nodule)

Definition: Adrenocortical heterotopias are microscopic nodules of adrenocortical tissue identified within placental tissue.

Clinical Context: Adrenocortical heterotopias are uncommon microscopic lesions discovered incidentally, ranging in size from less than 0.1 cm to 0.4 cm[1,7–10]. All have been solitary, and all have been identified in preterm third trimester placentas or term placentas. Because these nodules are found on microscopic examination of randomly sampled placental sections, the majority must go undiagnosed, and this lesion is probably more common than reported.

Proposed Pathogenesis: Heterotopic adrenocortical tissue located outside the region of the urogenital tract is difficult to explain by embryology; however, several theories have been suggested. One theory suggests that these heterotopias result from a migration of a portion of coelomic mesenchymal cells, which differentiate into adrenal primordia and become integrated into the extracoelomic mesenchyme of the placenta[6]. Others have theorized that these heterotopias result from embolic spread of adrenal precursor cells via fetal vascular "shortcuts"[9]. Pluripotent cells with adrenocortical differentiation may also migrate from the embryonic yolk sac to the placenta (choristoma). Still others have suggested that adrenocortical tissue in the placenta forms locally from multi-potential placental-derived stem cells, possibly related to genetic or epigenetic alterations, facilitating formation of adrenocortical tissue[10].

Gross Features: Adrenocortical heterotopias have not been identified grossly.

Microscopic Features: Heterotopic adrenocortical nodules usually present in stem villi, but have also been described in a subchorionic location[10]. They are typically partially bordered by fibrin, simulating a pseudocapsule[1]. They are composed of large polyhedral cells with prominent cell membranes; clear to eosinophilic granular cytoplasm; small, centrally placed nuclei with occasional binucleation; and fine vasculature (Figures 23.3 and 23.4). Lipofuscin pigment is typically present[1]. Mitotic activity and significant nuclear atypia are absent. Cytologically, the cells resemble the zona fasciculata, but the cell configuration is patternless, and lacks the typical zonation pattern of the adrenal cortex[10].

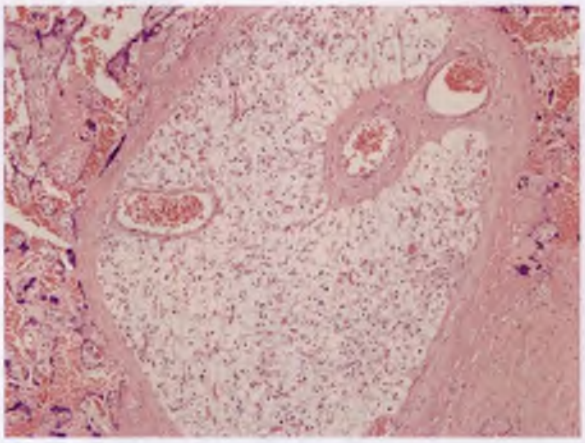

Figure 23.3 This microscopic nodule of adrenocortical cells is present within a stem villus and is partially surrounded by a thin rim of fibrin.

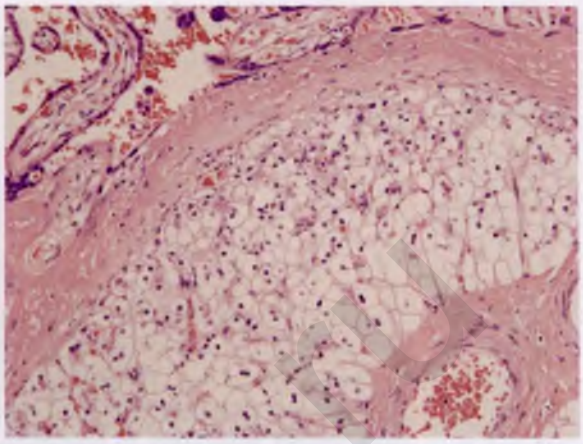

Figure 23.4 The adrenocortical cells are large and polyhedral with granular to clear cytoplasm, prominent cell membranes, small centrally placed nuclei with occasional binucleation, and fine vasculature.

Ancillary Diagnostic Testing: Immunohistochemically, the adrenocortical cells are positive for inhibin alpha, Melan-A, and cytokeratin Cam 5.2[10]. The cells have also been shown to express dehydroepiandrosterone sulfate (DHEA-S)[7]. Because adrenocortical heterotopias are minute, immunohistochemical staining may not be possible; however, the diagnosis can generally be made on hematoxylin and eosin-stained slides.

Prognostic Implications: Adrenocortical heterotopias are incidental findings, generally not associated with adverse pregnancy outcome or fetal disease. The expression of DHEA-S and inhibin alpha suggests that the cells are functional, but there is no evidence that they can undergo hyperfunctional or neoplastic change[10]. Although three of the reported adrenocortical heterotopias have been in twin placentas[1,8,9], and one in the placenta of an infant with Turner syndrome[1], it remains to be determined if this is more than coincidental until more cases are reported.

Knowledge Gaps: The embryogenesis of these lesions remains unclear. If these are heterotopias, the migratory pathways of the adrenocortical cells remain obscure.

Teratoma

Definition: Nodular masses of disorganized mature tissue elements, including ectodermal, mesodermal, and endodermal tissues, occurring between the amnion and chorion on the fetal surface of the placenta, or attached to the umbilical cord.

Clinical Context: *Placental teratomas* are rare and usually incidental findings[11–14]. Most have projected from the fetal surface, possibly attached by a pedicle, and are smooth, round, or oval, measuring 2.0 to 7.5 cm in diameter[11]. If there is an umbilical cord, and there are axially oriented skeletal structures, then these are classified as acardiac fetuses, as the diagnosis of teratoma is reserved for masses in which the tissue elements are totally disorganized[14]. The distinction between teratomas and acardiac fetuses, however, is an area of dispute, with some noting a continuum in the features of placental teratoma and acardiac fetus in reported cases, and also noting that lack of an umbilical cord does not exclude an acardiac fetus[15].

Proposed Pathogenesis: Teratomas are believed to arise from primordial germ cells that have migrated from the dorsal wall of the yolk sac to the placenta during the first trimester[16]. Germ cells migrate along the mesentery of the primitive gut to the genital ridges, and it is possible that with the evagination of the primitive gut into the umbilical cord in the first trimester, germ cells migrate from the gut into the cord substance. This could give rise to a cord teratoma, or continue to migrate into the connective tissue between the amnion and chorion[16].

Gross Features: The lesions are solid and smooth, oval to round, and project from the surface of the chorionic

plate, located between the amnion and chorion. The nodule is not supplied by large blood vessels, but instead blood supply is generally from a branch of a chorionic plate fetal artery[11–14]. By definition, teratomas do not have an umbilical cord (otherwise they are classified as acardiac fetuses).

Microscopic Features: Placental teratomas have features typical of a mature teratoma, namely an admixture of totally disorganized mature tissues such as skin appendages, adipose tissue, gastrointestinal epithelium, skeletal muscle, neural elements, cartilage, and bone[11–14].

Ancillary Diagnostic Testing: There are currently no accepted ancillary techniques to confirm a diagnosis of placental teratoma.

Prognostic Implications: Whether a placental mass is classified as a teratoma or an acardiac fetus, the clinical significance depends upon its circulation interfering with the growth of the "pump" twin. Reported placental teratomas have been small and supplied by small blood vessels, and have not been demonstrated to affect the course of pregnancy or fetal development[11–14].

Knowledge Gaps: The existence of teratomas remains unproven, as do widely accepted means of distinguishing teratomas, if such entities truly exist, from acardiac fetuses.

Yolk Sac Tumor

Definition: A *yolk sac tumor of the placenta* is a morphologically heterogeneous primitive neoplasm exhibiting multiple types of endodermal differentiation that can include primitive intestinal tissue, hepatic tissue, or yolk sac vesicles.

Clinical Context: Only two cases have been reported, the first consisting of two intraparenchymal nodules (3.0 and 5.5. cm) in the placenta of a term newborn with Beckwith-Wiedemann syndrome[17], and the second a single nodule (4.0 cm) in the placenta of an otherwise normal term infant[18].

Proposed Pathogenesis: Although the possibility has been considered that these represent monodermal teratomas expressing pure endodermal differentiation, placental teratomas are typically located between the amnion and chorion, and by definition are composed of tissue derived from all three germ layers[18]. As with hepatic and adrenal tissue within the placenta, possible pathogeneses of placental yolk sac tumors may include origin from displaced yolk sac elements[2], or local formation from multi-potential placental-derived stem cells[10].

Gross Features: Reported tumors are well circumscribed, predominantly solid with few small cysts, with variegated cut surfaces and without hemorrhage or necrosis.

Microscopic Features: One of the tumors displayed mesenchyme-like and enteroid patterns (gland-like structures, resembling vitelline vesicles)[17], while the second displayed divergent endodermal differentiation with a primitive endodermal component, a well-differentiated enteric glandular component, and a hepatic component, within a mesenchyme-like myxoid background[18] Both exhibited focal hematopoietic cells.

Ancillary Diagnostic Testing: Immunohistochemical staining for alpha-fetoprotein is positive[17,18].

Prognostic Implications: No germ cell tumors have been reported at other sites in either the mothers or the infants.

Knowledge Gaps: The pathogenesis of these very rare tumors remains uncertain.

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Chapter

24 Lysosomal Storage Disease, Bartter Syndrome, and Mimics

Raymond W. Redline

Vacuolation of Villous Trophoblast (Lysosomal Storage Disorders, Other)

Definition: The 5 specific lysosomal storage disorders (LSD) listed below are characterized by marked cytoplasmic expansion and vacuolation of the syncytiotrophoblast[1]. Extravillous trophoblast, amnionic epithelial cells, and villous macrophages (Hofbauer cells) are also affected.

1. Galactosialidosis (protective protein/ Cathepsin A deficiency)
2. I cell disease/mucolipidosis type II (N-acetyl glucosaminephosphoryl transferase α/β deficiency)
3. GM1-gangliosidosis (beta-galactosidase deficiency)
4. Sialidosis/mucolipidosis type I (alpha neuraminidase deficiency)
5. Infantile sialic acid storage disorder/ Salla disease, (Sialin deficiency)

Clinical Context: Overall, LSD affect 1 in 5–7000 individuals and account for 48 percent of specific diagnoses of neurodegeneration[2]. Most LSD first manifest in later childhood or adolescence, but a subgroup of approximately 14 disorders can present with hydrops fetalis and fetal ascites[3]. The etiology for hydrops in these cases is multifactorial and may include hepatosplenomegaly leading to cardiac failure via impaired venous return, hypoproteinemia, abnormal erythropoiesis, and hypersplenism. The specific histologic findings detectable by routine placental examination in the 5 LSD listed above can expedite specific diagnosis and treatment in cases presenting with hydrops fetalis and other critical neonatal conditions, and occasionally will detect occult disease in asymptomatic newborns, allowing early intervention[1,4].

Proposed Pathogenesis: LSD are a pathophysiologically diverse group of disorders that share the defining feature of excessive accumulation of undegraded macromolecules and/or monomer catabolic products within the endosomal-autophagocytic-lysosomal compartment of affected cells[2]. This accumulation can be due to a wide variety of cellular mechanisms including enzyme deficiencies, abnormal macromolecular trafficking, and mutations in nonenzymatic cytoplasmic or membrane lysosomal proteins. Downstream consequences of these diverse defects include cellular swelling, failure to reconstitute functional lysosomes, and failure to clear dysfunctional mitochondria by autophagy leading to the generation of toxic reactive oxygen intermediates.

Gross Features: LSD with villous trophoblast vacuolation are often associated with hydrops fetalis, in which case the placentas will generally be large, pale, and have a decreased fetoplacental weight ratio. Gross features to look for in the delivered fetus/infant include coarse facies, hepatosplenomegaly, and skeletal abnormalities. Several LSD, including galactosialidosis and I-cell disease, can also show rhizomelic shortening of long bones and stippled epiphyses (chondrodysplasia punctata)[5].

Microscopic Features: Placentas from the 5 LSD listed above show a nonspecific pallor at scanning magnification due to a combination of hydrops and vacuolated fetal cells (Figure 24.1), which should prompt more careful inspection at higher power. Upon closer examination, the syncytiotrophoblast layer is markedly thickened with an increased number of uniformly spaced nuclei. Cytoplasm is increased in volume and shows diffuse vacuolation that ranges from a microvesicular pattern to complete cytoplasmic clearing (Figure 24.2 and 24.3). Other situations associated with vacuolated syncytiotrophoblasts that can mimic LSD include rare chromosomal abnormalities such as trisomy 14 (Figure 24.4), cellular artifacts introduced by freezing the placenta, and use of hypertonic saline or prostaglandins for pregnancy termination. Microvesicular steatosis of unknown etiology is also occasionally encountered (Figures 24.5 and 24.6; see next section)[6,7]. Other placental cell types are also

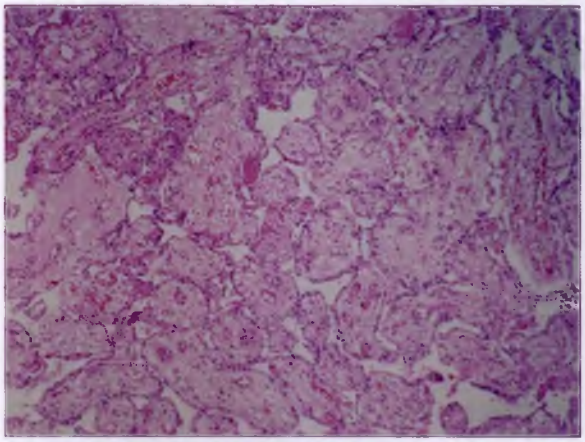

Figure 24.1 Hydrops fetalis with vacuolated villous trophoblast and macrophages.

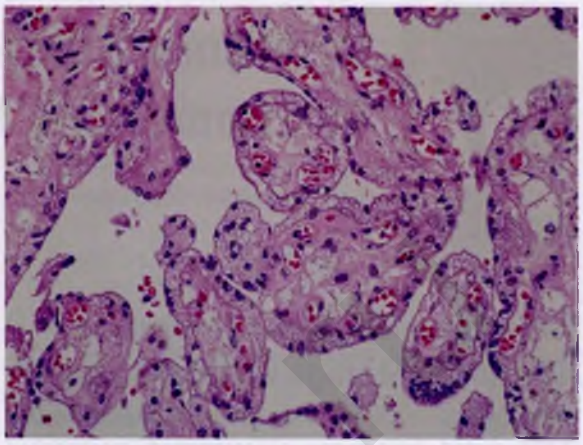

Figure 24.2 Villous trophoblast vacuolation in galactosialidosis.

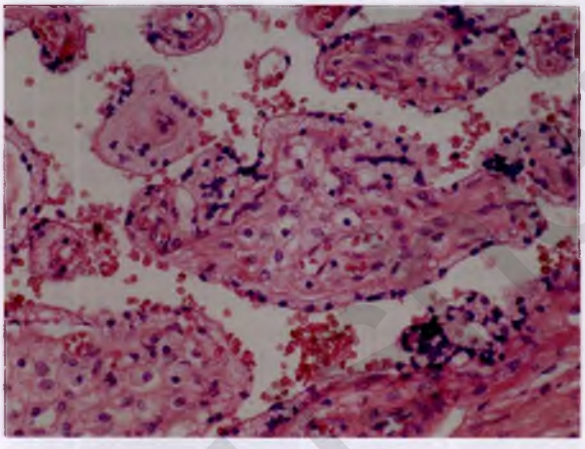

Figure 24.3 Villous trophoblast vacuolation in I-cell disease. Note the prominent vacuolated villous Hofbauer cells in stroma.

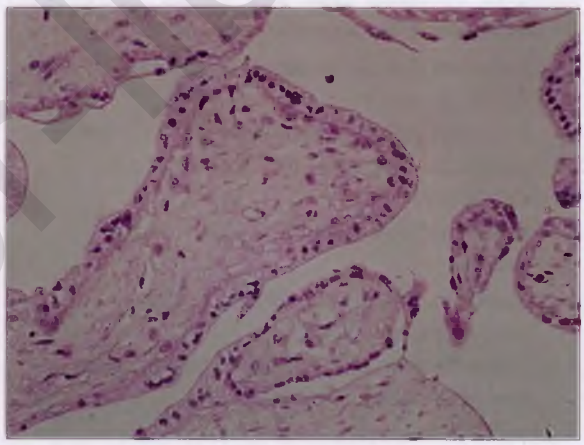

Figure 24.4 Villous trophoblast vacuolation in trisomy 14.

affected in LSD, including amnionic epithelium (Figure 24.7), extravillous trophoblast (Figure 24.8), and villous Hofbauer cells (Figure 24.3). However, with the exception of glycogen storage disease IV, which shows cytoplasmic polyglucosan inclusions limited to extravillous trophoblast[8], vacuolation in these other cell types has a poor predictive value for LSD. Amongst the diagnostic pitfalls are (1) microvesicular changes in amnionic epithelial cells with fetal gastroschisis (Figure 24.9)[9], (2) cytoplasmic vacuolation in immature (transitional) extravillous trophoblasts (Figure 24.10, see discussion in Chapter 5), and (3) vacuolated villous macrophages (Hofbauer cells), which are prominent in many immature placentas.

Ancillary Diagnostic Testing: Special stains such as PAS and Alcian blue stains are variably positive and do not generally add useful information. Oil Red O staining of nonembedded formalin fixed or fresh tissue suggests Wolman or cholesterol ester storage diseases, but some positively staining cases remain unexplained (Figure 24.5 and 24.6)[7]. Electron microscopy demonstrating lack of membrane bound vacuoles, lamellar bodies, and/or membrane bound lipid inclusions can help exclude LSD. Ultrastructural analysis of chorionic villus biopsies in patients at risk for LSD has been used as an ancillary technique for prenatal diagnosis[1,10,11]. However, findings are somewhat inconsistent. Multiple reports document characteristic findings for MPS-7 (Sly disease), Niemann-Pick A, MPS-1 (Hurler disease), and GSD2 (Pompe disease). Reported findings for other conditions,

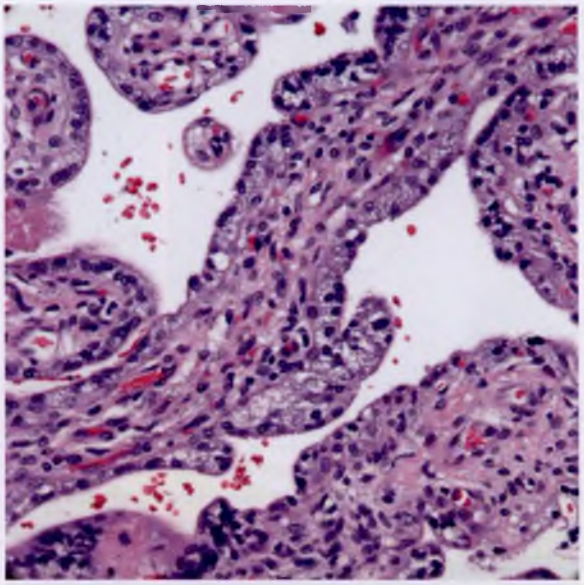

Figure 24.5 Idiopathic villous trophoblast vacuolation secondary to microvesicular steatosis. Image provided by Jerzy Stanek, Cincinnati Children's Medical Center, Cincinnati, OH.

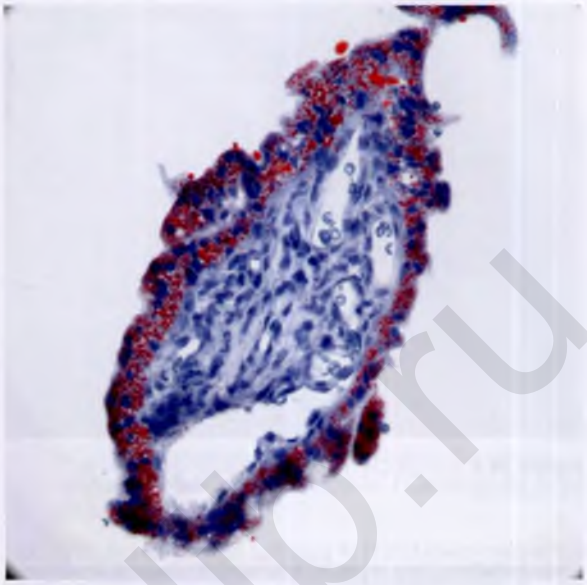

Figure 24.6 Idiopathic villous trophoblast vacuolation secondary to microvesicular steatosis (Oil Red O stain). Image provided by Jerzy Stanek, Cincinnati Children's Medical Center, Cincinnati, OH.

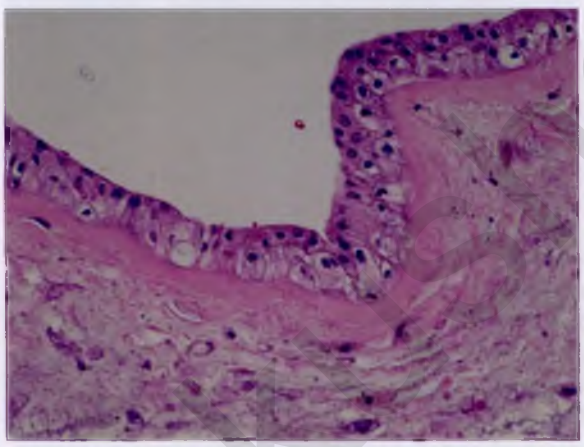

Figure 24.7 Amnionic epithelial vacuolation in galactosialidosis.

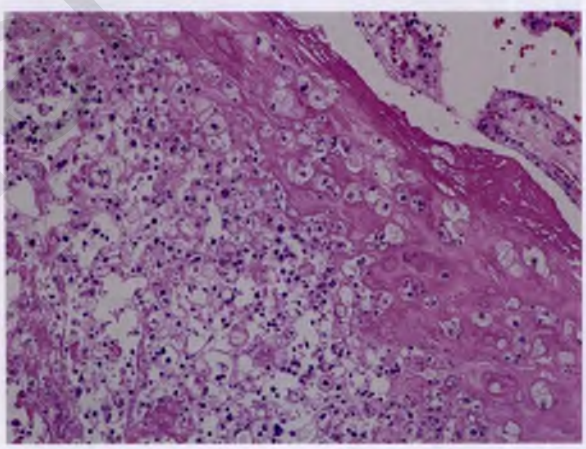

Figure 24.8 Extravillous trophoblast vacuolation in galactosialidosis.

including GM2 gangliosidosis, Fabry disease, and Gaucher disease, are more inconsistent[1,4,10,12]. Definitive diagnosis requires additional testing by urine electrophoresis, enzyme analysis of plasma, white blood cells, or fibroblasts, and/or DNA sequencing[3,13]. While it might seem that the latter would be definitive, variants of unknown significance can be encountered, and the final diagnosis may require a multidisciplinary approach that includes careful physical and radiologic examination, laboratory testing, and placental pathology.

Prognostic implications: LSD can lead to miscarriage, preterm delivery, hydrops fetalis, or IUFD. Accurate diagnosis can prevent recurrence and allow genetic counselling for family members. Specific diagnosis also provides important prognostic information as to the expected disease trajectory. Significant advances are on the horizon for treatment of LSD, so early diagnosis will likely be even more important in the future[14].

Knowledge Gaps: Many metabolic diseases, particularly LSD, have a severe early infantile presentation, but

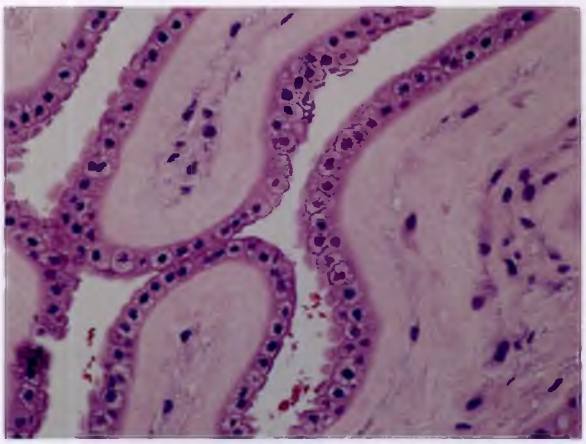

Figure 24.9 Amniotic epithelial vacuolation secondary to gastroschisis.

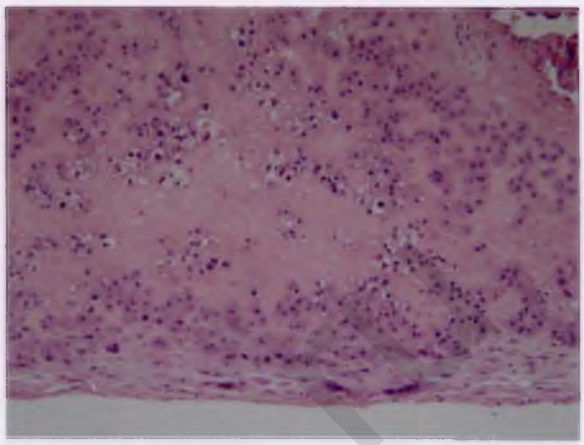

Figure 24.10 Vacuolated immature (transitional) extravillous trophoblast.

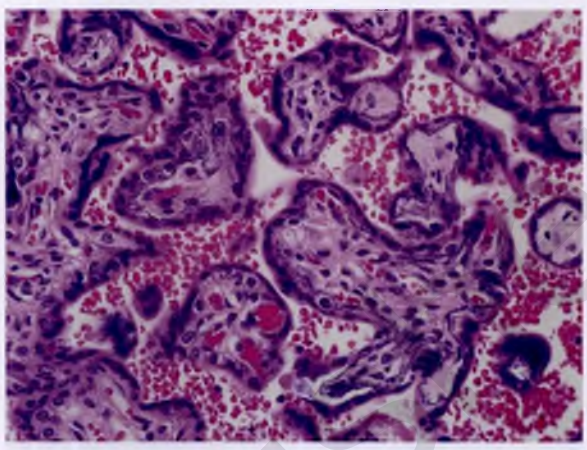

Figure 24.11 Villous trophoblast basement membrane mineralization in fetal *Bartter syndrome*.

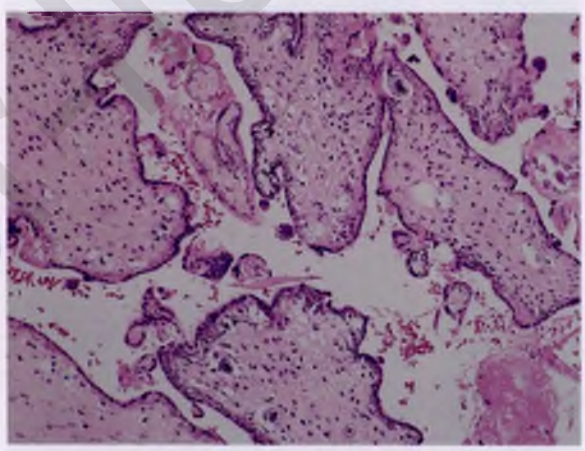

Figure 24.12 Villous trophoblast basement membrane mineralization in trisomy 21.

lack definite placental findings by light microscopy. Whether the pathologic abnormalities in the placenta have specific effects on placental function is unknown.

Mineralization of Villous Trophoblast Basement Membrane (Bartter Syndrome, Other)

Definition: Linear deposits of calcium and/or iron along the villous trophoblastic basement membrane are typically seen in cases of fetal *Bartter syndrome* (Figure 24.11)[15,16], but may also be seen in other pathologic conditions (Figure 24.12).

Clinical Context: Fetal Bartter syndrome presenting in the antenatal period is an autosomal recessive disorder caused by homozygous or compound heterozygous mutations in the ATP dependent potassium channel ROMK gene (KCNJ1) at chromosome 11q24. Defective gene function leads to decreased sodium chloride reabsorption in the proximal loop of Henle, resulting in polyuria and increased amniotic fluid volume (polyhydramnios), hypercalciuria leading to nephrocalcinosis, hypocalcemia, osteopenia, and elevated levels of prostaglandin E2 possibly contributing to an increased incidence of preterm labor[17].

Proposed Pathogenesis: Abnormal fetal renal tubular absorption of sodium chloride leads to loss of the intrarenal diffusion gradient required for calcium reabsorption resulting in hypocalcemia. It has been

suggested that this promotes supraphysiologic levels of calcium uptake by villous trophoblast at the maternal fetal interface resulting in dystrophic mineralization of the basement membrane. However, KCNJ1 is also expressed in syncytiotrophoblast, (www.proteinatlas.org/ENSG00000151704-KCNJ1/tissue/placenta) so a primary effect of the mutation on trophoblast function is not excluded.

Gross Features: For reasons that are not clear, placental weight is increased in most reported cases of fetal Bartter syndrome[15,16]. Increased weight in this context does not appear to be associated with macrosomia, maternal glucose intolerance, delayed villous maturation, or hydrops fetalis (see Chapter 16).

Microscopic Features: Mineralization of the villous trophoblastic basement membrane is not specific for Bartter syndrome. It can also be seen with preterm stillbirth, chromosomal abnormalities including trisomy 21, hydrops fetalis, and severe cases of both maternal and fetal vascular malperfusion. A differentiating feature is that villous morphology in these other disorders is usually abnormal while in Bartter syndrome the mineralization affects otherwise normal villi (Figure 24.11). Important caveats are (1) the amount of mineralization in Bartter syndrome cases can be quite variable from case to case[18] and (2) a diagnosis of Bartter syndrome is unlikely in the absence of clinical polyhydramnios and/or a positive family history.

Ancillary Diagnostic Testing: Controversy exists regarding the nature of the precipitated salts in Bartter syndrome. Histochemical stains indicate that they are at least in part composed of calcium. However, some authors have found a variable component of ferric iron[15,16]. A presumptive antenatal diagnosis of Bartter syndrome can be made when polyhydramnios is accompanied by abnormal electrolytes (chloride, sodium, and calcium) in the amniotic fluid (elevated) and maternal urine (reduced). Definitive diagnosis requires molecular genetic testing[17].

Prognostic Implications: Infants with antenatal Bartter syndrome generally show severe salt wasting, metabolic alkalosis, and failure to thrive. Some develop the hyperprostaglandin E syndrome characterized by pain, fever, and diarrhea. Life threatening arrhythmias secondary to hyperkalemia may also occur. Genetic counselling is indicated once the impression of fetal Bartter syndrome is confirmed. Early diagnosis in subsequent pregnancies provides the opportunity for indomethacin treatment, which may prevent nephrocalcinosis[18].

Knowledge Gaps: The pathogenesis and chemical composition of trophoblast basement membrane mineralization in Bartter syndrome and other conditions remain unclear.

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Chapter 25

The Pathology of Monochorionic Placentation

Monique E. De Paepe

THE MONOCHORIONIC DIAMNIOTIC TWIN PLACENTA

General Features of Monochorionic Diamniotic Twin Placentas

Definition: Twin placenta characterized by the presence of a single chorion shared by both twins. Monochorionic twins may have separate amnions (diamniotic-monochorionic placentation) or a common, single amniotic cavity (monoamniotic-monochorionic placentation).

Clinical context: The overall perinatal mortality and morbidity rates of twins are 3 to 7 times higher than those of singletons, in large part explained by their higher prematurity rates. Monochorionic twins (20–25 percent of all twins) face the highest risk[1]. Monochorionic twins share a single placenta and are virtually always connected through intertwin choriovascular anastomoses. These anatomic characteristics form the basis of unique complications of monochorionic pregnancies, such as twin-to-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), and twin reversed arterial perfusion (TRAP) syndrome. Monoamniotic monochorionic twins are, in addition, at risk for umbilical cord entanglement.

Knowledge of chorionicity (and amnionicity) is important for optimal prenatal management of multiple gestations. Sonographic clues to chorionicity include gender (fetal gender discordance indicates dichorionicity); placental site characteristics (separate placental sites indicate dichorionicity); thickness and layering of the intertwin membrane (thick, three- or four-layered dividing membrane indicates dichorionicity); and shape of the junction between dividing membrane and placenta. The "lambda" or "twin peak" sign, a wedge-shaped, curved projection of echodense chorionic villi and trophoblast into the base of the dividing membrane, reflects dichorionicity. The "T-sign," created by the near-perpendicular junction between intertwin membrane and chorionic plate, suggests monochorionicity. A single amniotic sac and closely inserted umbilical cords suggest monoamnionicity.

Chorionicity refers to the type of placentation; the closely related term "zygosity" refers to the type of conception. It has traditionally been asserted that monochorionicity implies monozygosity. However, the sporadic occurrence of dizygotic monochorionic (diamniotic) twinning is well-documented, usually associated with confined tissue and/or blood chimerism, and usually – but not always – in pregnancies achieved by assisted reproductive technology[2,3]. Accurate determination of zygosity is therefore indicated in all multiple gestations, as assumptions regarding zygosity based on antenatal ultrasound findings or postnatal placental examination may be unreliable.

Proposed Pathogenesis: According to traditional models of twinning, dizygotic (nonidentical, fraternal) twins (about 70 percent of twins) result from fertilization of two distinct ova by two separate sperm cells, whereas monozygotic (so-called 'identical') twins (about 30 percent of twins) are the product of division of a zygote created by fertilization of one ovum by one sperm cell[4]. In the widely accepted – but mechanistically unproven – "fission" or "splitting" model of monozygotic twinning, the number of fetuses, chorions, and amnions is determined by the timing of division of the zygote. Early division, within the first 3 days post-fertilization (70 percent of monozygotic twins) usually results in dichorionic placentation. Division in the blastocyst stage, after formation of the chorion but before formation of the amnion (3–9 days post-fertilization; 25 percent) results in diamniotic-monochorionic placentation. Late division (8–12 days post-fertilization; 2 percent) leads to monoamniotic-monochorionic placentation, whereas even later splitting (13–16 days post-fertilization; 1:100,000) results in conjoined monoamniotic-monochorionic twinning[5].

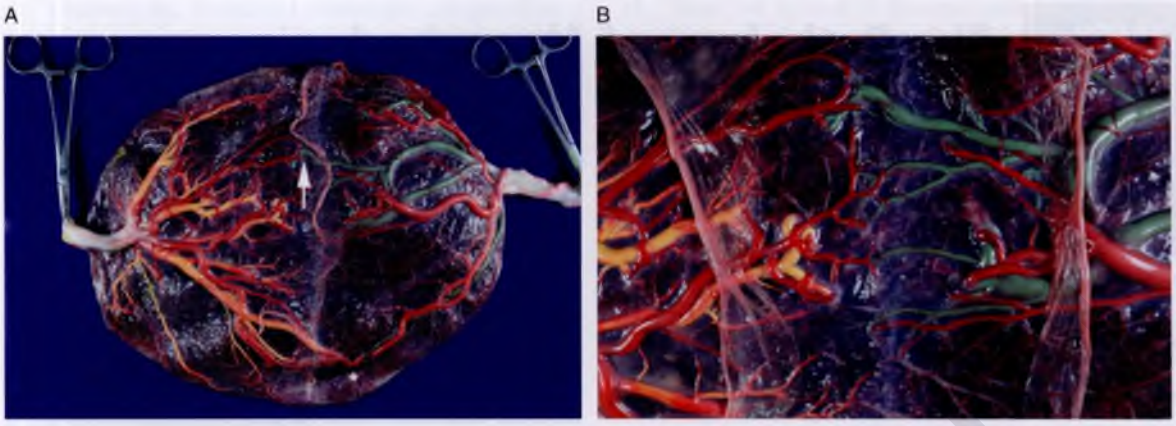

Figure 25.1 Diamniotic-monochorionic twin placenta. (a) Overview showing thin intertwin membrane. Chorionic vasculature is dye-injected using the following color code. Left twin: artery red, vein yellow; right twin: artery red, vein green. Due to presence of an AA anastomosis, the arterial bed of both twins shares the same color (red). Asterisk: AA anastomosis; arrow: AV anastomosis; from left-to-right. (b) Closer view of the vascular equator. The intertwin membrane has been retracted to the side, exposing bare chorion and several left-to-right AV anastomoses.

Cases of atypical twinning, such as chimeric twins, phenotypically discordant monozygotic twins, mirror-image twins, and polar body twins, have prompted critical re-examination of the traditional postzygotic fission models of monozygotic twinning[6]. Alternative theories have been proposed, such as a "fusion" model, according to which monozygotic twinning occurs at the first zygotic cleavage division, with chorionicity and amnionicity determined by the degree of subsequent embryonic membrane fusion within the zona pellucida[7]. At present, both the fission and fusion models remain controversial and unsubstantiated[6].

The stimuli for monozygotic twinning are incompletely understood. Evidence suggests a two- to five-fold rise in the incidence of monozygotic twinning in pregnancies achieved by assisted reproductive techniques (ART), compared with spontaneous conception[6,8–10]. This supports a role for environmental influences, possibly related to micromanipulation or cell culture techniques, in combination with maternal age and infertility-associated intrinsic anomalies[11–13]. In addition, genetic factors may play a role, as suggested by the occurrence of familial monozygotic twinning[14] and the abnormally high monozygotic twinning rates in some genetic syndromes, such as Beckwith-Wiedemann and Opitz G/BBB syndromes[15].

Gross Features: The monochorionic twin placenta is a single-disc twin placenta, with or without intertwin (or dividing) membrane, the first corresponding to diamniotic and the latter to monoamniotic monochorionic placentation. In the presence of an intertwin membrane, a diamniotic-monochorionic twin placenta is distinguished from a fused diamniotic-dichorionic twin placenta by examination of the intertwin membrane and chorionic plate vasculature. A thin, semitranslucent, two-layered intertwin membrane, loosely attached to the chorionic plate, is diagnostic of diamniotic-monochorionic placentation. In contrast, a relatively opaque, three- or four-layered intertwin membrane with ridge-like attachment to the chorionic plate, which clearly separates the chorionic vascular beds of each twin, is diagnostic of dichorionic placentation (Figure 25.1)[16]. Reference values for weights of twin placentas have been established[17,18].

Almost all monochorionic placentas (>95 percent) exhibit intertwin vascular anastomoses crossing the intertwin membrane (Figure 25.1–3)[19–21]. The chorionic vessels are categorized based on their (near-) constant anatomic relationships: chorionic arteries virtually always course superficial to their accompanying veins. Vascular communications between monochorionic twins can be artery-to-artery (AA), vein-to-vein (VV) or artery-to-vein (AV). The AA and VV anastomoses are superficial: they form a direct communication between homonymous vessels from each twin without penetrating the chorionic plate (Figure 25.2). In contrast, AV anastomoses virtually always occur deep within the parenchyma at the villous capillary

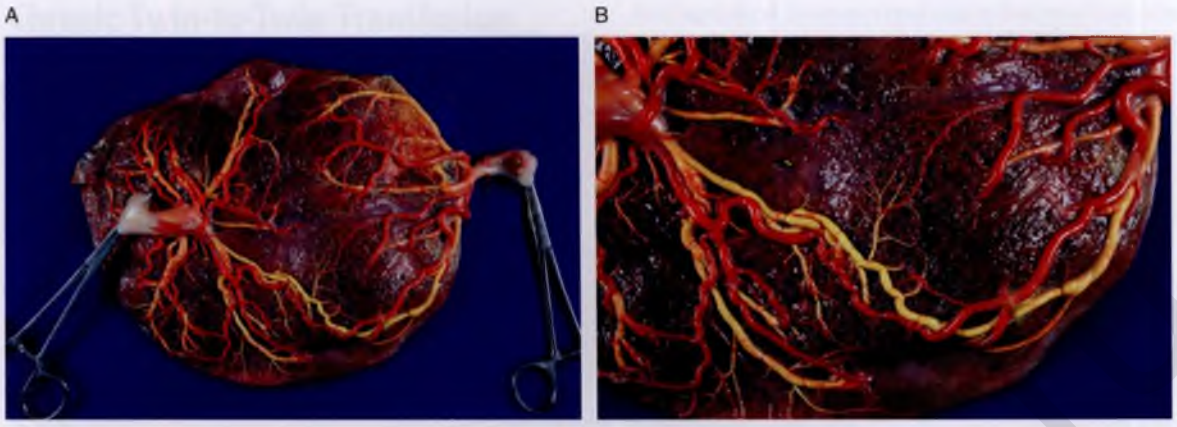

Figure 25.2 Diamniotic-monochorionic twin placenta with AA and VV anastomoses. (a) Overview showing placenta following vascular dye injection. Due to the presence of AA and VV anastomoses, the vascular beds of both twins share the same color (artery: red; vein: yellow). The intertwin membrane has been removed prior to injection. (b) Closer view of the AA (red) and VV (yellow) anastomoses, which form a direct, superficial connection between both cords.

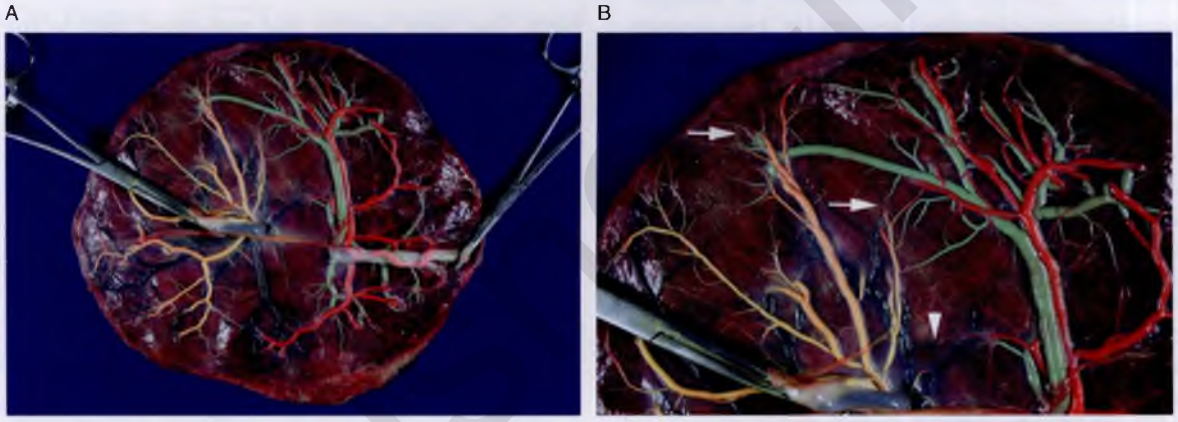

Figure 25.3 Diamniotic-monochorionic twin placenta without AA or VV anastomoses. (a) Overview showing placenta following vascular dye injection using the following color code: left twin: artery yellow, vein blue; right twin: artery red, vein green. Due to the absence of AA or VV anastomoses, the arterial and venous beds of both twins have different colors. The intertwin membrane has been removed prior to injection. (b) Closer view of the vascular equator showing left-to-right AV anastomoses (arrows) and a right-to-left AV anastomosis (arrowhead).

level and are recognized by the chorionic penetration of an unpaired artery of one twin in close proximity to an unpaired vein of the opposite twin (Figure 25.3). AV anastomoses are obligatorily unidirectional. AA and VV anastomoses are bidirectional and allow flow in either direction, depending on pressure gradients between twins. Superficial AA and VV anastomoses are thus believed to be able to compensate for flow imbalances generated by nonequilibrated AV anastomoses.

Large-sized AA and VV anastomoses can usually be identified by gross examination of the non-injected placenta, or by simple injection of an umbilical or chorionic artery or vein with air or saline solution. More detailed vascular injection studies using color-coded dyes may be indicated for accurate delineation and categorization of smaller vessels and complex patterns of intertwin AV anastomoses, especially in pregnancies with unanticipated outcome or following laser ablation for TTTS[16,21,22].

Microscopic Features: Microscopic examination of the intertwin membrane allows confirmation of chorionicity. The dividing membrane of diamniotic-

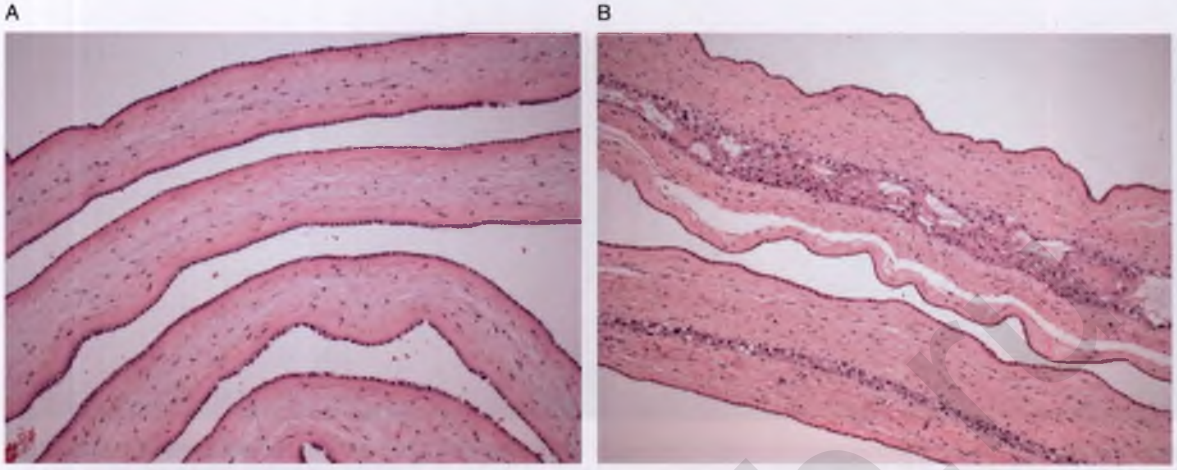

Figure 25.4 Intertwin membrane of monochorionic and dichorionic twin placentas. (a) Intertwin membrane of a diamniotic-monochorionic twin placenta showing direct apposition of two amnion layers without intervening chorion. (b) Intertwin membrane of a diamniotic-dichorionic twin placenta showing separation of amnion layers by interposed chorion layers.

monochorionic placentas consists of two amnion layers, without interposed chorion (Figure 25.4a), whereas in dichorionic placentas the two amnion layers are separated by chorionic tissue (Figure 25.4b). Distinct histopathologic parenchymal characteristics between twin territories may explain birth weight discordance, discordance in hematologic parameters, and other phenotypic differences between so-called identical twins.

Ancillary Diagnostic Testing: Although monochorionicity remains an excellent proof of monozygosity, rare exceptions have been described involving dizygotic monochorionic twinning[2,3]. Determination of monochorionic placentation status should therefore be regarded as a screening tool, rather than unequivocal evidence of monozygosity[23]. Further genotyping is especially recommended when monochorionic twins have a dissimilar somatic phenotype, and following artificial reproduction[23]. Definitive zygosity determination relies on genetic markers such as blood group testing or, preferably, PCR analysis of variable microsatellite markers using DNA extracted from skin biopsy, umbilical cord tissue, or buccal smear. Possible pitfalls in interpretation must be taken into account, such as those created by postzygotic mutations and blood mosaicism[23].

Prognostic Implications: Independent of zygosity, monochorionicity is associated with higher perinatal mortality and with increased incidence of preterm birth, low birth weight, and prolonged stay in the neonatal intensive care unit compared to dichorionic twin pregnancies. The overall perinatal mortality is ~12 percent in monochorionic twins compared to 2–5 percent in dichorionic twins, and mortality is even higher in monoamniotic twins (between 10 percent and 40 percent)[24–26]. Monochorionic twin pregnancies are further susceptible to a specific set of complications, as described below. Because nearly all monochorionic pregnancies have connections between the two choriovascular beds, death of one twin affects the outcome of the surviving co-twin[27]. Consequences for the surviving co-twin include death, survival with cerebral impairment or other vascular disruptions, or preterm delivery with its attendant sequelae.

Knowledge Gaps: The mechanisms underlying monozygotic twinning remain incompletely understood. The exact contributions of placental and choriovascular characteristics to the specific complications of monochorionic twinning are unclear. Unbiased studies are needed to estimate the impact of twinning and twinning type on pregnancy outcome and on long term growth and neurocognitive function. The relative contributions of genetic, epigenetic, mitochondrial, and environmental factors on phenotypical differences between monozygotic twins remain poorly defined.

Chronic Twin-to-Twin Transfusion Syndrome (TTTS) Also Known as Twin Oligohydramnios-Polyhydramnios Sequence (TOPS)

Definition: A complication of monochorionic twinning, characterized by chronic fetofetal blood transfusion from one twin ("donor") to the other ("recipient") through placental vascular communications. This unbalanced shift of blood volume results in hemodynamic imbalance, oligohydramnios in the donor and polyhydramnios in the recipient. The chronic form of TTTS, characterized by oligohydramnios-polyhydramnios, needs to be distinguished from acute forms of TTTS (see below).

Clinical Context: Severe chronic twin-to-twin transfusion syndrome (TTTS) complicates 9–15 percent of diamniotic-monochorionic twin pregnancies[28,29]. The diagnosis of TTTS is based on strict antenatal ultrasound criteria including: 1) monochorionicity, and 2) concomitant oligohydramnios in the donor twin (deepest vertical pool in amniotic sac ≤ 2 cm) and polyhydramnios in the recipient co-twin (deepest vertical pool ≥8 cm; in Europe ≥10 cm after 20 weeks)[30,31]. Intertwin growth discordance and intrauterine growth restriction often accompany TTTS but are not independent diagnostic criteria.

Although TTTS may develop at any time in gestation, the syndrome typically presents in the second trimester of pregnancy, between 16 and 26 weeks' gestation, and is detected by observation of amniotic fluid discordance during routine ultrasound follow-up of a diamniotic-monochorionic pregnancy. The recipient twin may display a spectrum of echocardiographic findings described as TTTS-related cardiomyopathy[32,33].

Staging of TTTS, based on ultrasound studies, is used to determine prognosis and optimal management strategy. Increasing stages of TTTS severity according to the most widely used Quintero system include amniotic fluid volume discordance (stage 1); nonvisualization of filling of the (donor) bladder (stage 2); critically abnormal Doppler studies (stage 3); fetal hydrops in either twin (stage 4); and (impending) fetal demise (stage 5)[29,30]. More recent adaptations of the Quintero staging system include a variety of echocardiographic and hemodynamic indices[34–36].

The term "TTTS" traditionally refers to the often severe, chronic condition and needs to be distinguished from several acute forms of intertwin transfusion. Acute *perimortem* TTTS occurs following intrauterine death of one monochorionic twin and is caused by exsanguination from the surviving twin into the low-pressure circulation of the dead or dying co-twin[37]. Acute *peripartum* (or *perinatal*) TTTS may occur during birth and is caused by acute shifts of blood volume between twins resulting from blood pressure differences associated with delayed cord clamping, uterine contractions, or changes in fetal position around delivery. The clinical presentation of acute peripartum TTTS ranges from subtle intertwin differences in hemoglobin levels to frank hypovolemic shock in the donor twin and polycythemia in the recipient twin[37]. Both forms of acute TTTS are believed to be facilitated by large superficial AA and VV anastomoses. Acute peripartum TTTS is distinct from the more common postpartum placentofetal (as opposed to twin-to-twin, or fetofetal) transfusion that occurs when cord clamping of the first-delivered twin directs blood from the entire placenta to the co-twin through vascular anastomoses.

Proposed Pathogenesis: Chronic TTTS is a complex and incompletely understood condition with both placental and fetal contributions[38]. An intuitive, albeit somewhat simplistic model of TTTS proposes that the primary event is flow imbalance from donor to recipient across unidirectional AV anastomoses. If this flow imbalance is significant and not fully compensated by bidirectional AA anastomoses, the donor becomes hypovolemic and anemic, whereas the recipient becomes polycythemic and hypervolemic. These volume changes are believed to induce modulation of a variety of hormonal and biochemical regulators in both twins. The renin-angiotensin system is upregulated in the donor twin and downregulated in the recipient twin. Both twins are likely exposed to equally high renin levels through their shared circulation, which may contribute to cardiovascular anomalies in some recipient twins[39,40]. In addition, concentrations of atrial natriuretic peptide, brain natriuretic peptide and endothelin-1 are higher in the amniotic fluid of recipient twins compared to donor twins[41]. Although their exact mechanisms of action remain incompletely understood, dysregulation of these and other unidentified biochemical mediators likely play a role in a proposed exaggerated hemodynamic response to hyper- and hypovolemia in TTTS.

Gross Features: Although not pathognomonic, several choriovascular or anatomic placental characteristics have been linked to increased risk for development of TTTS in diamniotic-monochorionic twin gestations[38,42,43]. Pregnancies complicated by TTTS have a lower frequency of AA anastomoses than uncomplicated, non-TTTS monochorionic pregnancies (25–57 percent in TTTS versus >85 percent in non-TTTS placentas) (Figure 25.5)[38,42,43]. The relative paucity of AA anastomoses in TTTS placentas has contributed to the notion that these potentially bidirectional anastomoses have a protective role against the development of TTTS in monochorionic twin gestations, by compensating for hemodynamic imbalances created by uneven AV anastomoses[44].

In contrast to AA anastomoses, the frequency of VV anastomoses is higher in TTTS pregnancies than in non-TTTS pregnancies (38 percent versus 15–25 percent)[38,43–46]. In the subgroup of placentas without AA anastomoses, this difference is even more striking. In the absence of AA anastomoses, the prevalence of VV anastomoses is 32 percent in TTTS placentas versus 8 percent in non-TTTS placentas. This suggests VV anastomoses may play an adverse role in TTTS – especially in the absence of AA anastomoses – perhaps by acting as low-resistance functional AV anastomoses[47].

The contribution of the deep and obligatorily unidirectional AV anastomoses in the onset or perpetuation of TTTS remains unclear. In the absence of compensating AA anastomoses, AV imbalance directed from donor to recipient strongly correlates with the development of TTTS[38,43]. This combination of absent AA anastomoses and severe AV imbalance is highly specific for TTTS, but is seen in only a small minority of TTTS placentas (14 percent)[43]. The role of AV anastomoses in the vast remainder of monochorionic gestations is incompletely understood. Interestingly, TTTS has even been described in the absence of identifiable AV anastomoses[38,43,48]. It has been speculated that, in such cases, an AA anastomosis may have been converted into a functional AV anastomosis, for instance by stenosis of one twin's arterial compartment[48].

Finally, both peripheral cord insertion and uneven placental sharing have been linked to an increased risk for TTTS in monochorionic gestations. Peripheral (velamentous or marginal) cord insertion occurs in about 50 percent of TTTS gestations compared with about 30 percent of non-TTTS gestations. When cord insertion is discordant, it is virtually always the donor twin that has the peripheral cord insertion[38]. Markedly uneven placental sharing, defined as >25 percent intertwin difference in distribution of placental choriovascular territory, is seen in about 50 percent of TTTS gestations versus 25 percent of non-TTTS gestations[38]; the donor twin almost always has the smaller share.

Microscopic Features: The histology of TTTS placentas is non-specific, variable, and likely dependent on timing and stage of the syndrome. Pregnancies complicated by severe chronic TTTS may exhibit discordant villous maturation between twins. In such cases, villous maturation tends to be accelerated in the territory of the donor twin (Figure 25.6a), whereas the villi of the recipient may have increased numbers of distended, engorged capillaries (Figure 25.6b). The histology may be confounded by intrauterine demise of one or both twins, by associated placental anatomic factors (e.g. implantation anomalies, cord insertion), or by peripartum events such as acute transfusion.

Ancillary Diagnostic Testing: Large AA and VV anastomoses can usually be identified without dye injection. If indicated (e.g. by an atypical clinical course), the choriovascular intertwin anastomoses, including artery-to-vein anastomoses, may be examined in detail by vascular injection. As in every twin pregnancy, zygosity studies may be indicated. Hematologic analyses may

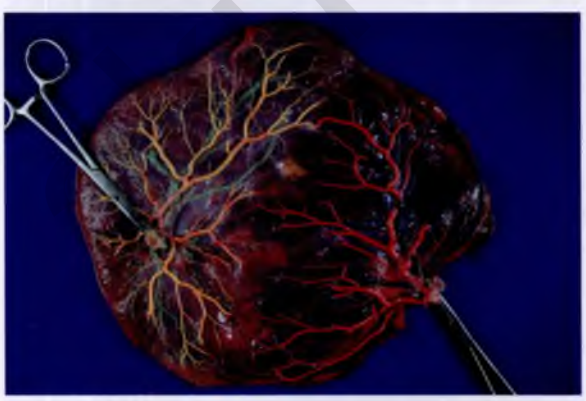

Figure 25.5 Placenta of twin pregnancy complicated by TTTS. AA anastomoses are absent. The donor twin (right) has a smaller placental territory and marginal cord insertion. Color code: left twin (recipient): artery yellow, vein green; right twin (donor): artery red, vein black). The intertwin membrane has been removed prior to injection.

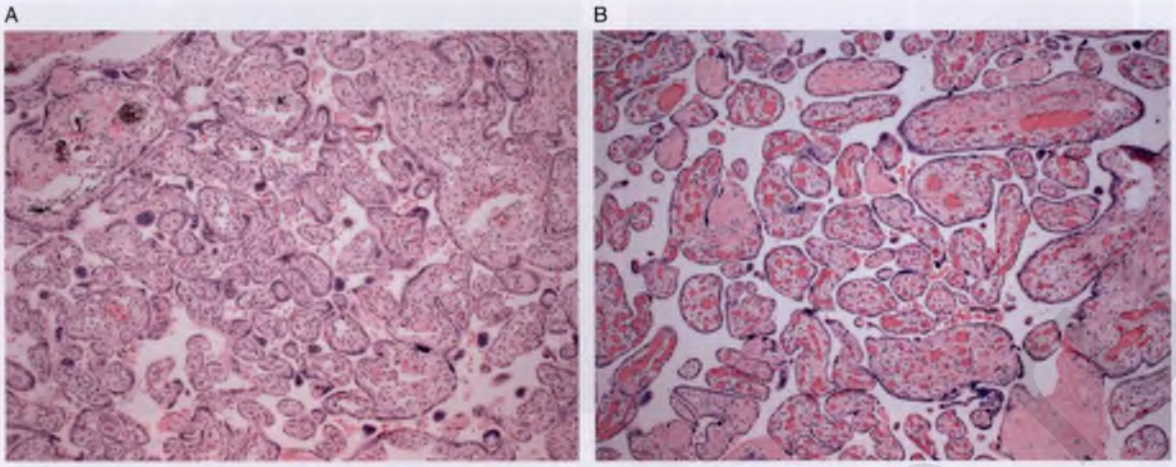

Figure 25.6 Histology of pregnancy complicated by TTTS (31 weeks' gestation). (a) Placental parenchyma of donor twin showing accelerated villous maturation and increased syncytial knots. (b) Parenchyma of recipient twin showing chorangiosis.

reveal intertwin differences in hemoglobin/hematocrit and extent of circulating erythroid precursors.

Prognostic Implications: The reported perinatal loss rate of untreated severe (i.e. stage 3 or higher) TTTS ranges between 70 percent and 100 percent, especially when the syndrome presents at <26 weeks' gestation[49,50]. Both fetuses are at risk for dying; in two-thirds of cases, demise of the donor twin occurs first. Because of the existing fetofetal shunts, the sudden drop in arterial perfusion pressure in the dying twin may result in a steal phenomenon from surviving to dead or dying twin, leading to profound hypotension in the surviving twin. Death or neurologic handicap of the co-twin following spontaneous or iatrogenic death of the first twin is common (10–30 percent)[51,52].

Periventricular leukomalacia is the most common brain lesion found in survivors of TTTS and may occur even in the absence of co-twin death. Other complications of TTTS include vascular disruptive events: limb necrosis, aplasia cutis and intestinal atresia virtually always affect the recipient twin, and are attributed to a combination of polycythemia and sluggish blood flow. Other TTTS-linked morbidities affecting the recipients include cardiomyopathy, pulmonary stenosis, hypertension and disseminated intravascular coagulation. Live born TTTS donors are at risk for renal tubular atrophy/renal tubular dysgenesis. Either twin can develop hydrops fetalis; the donor because of anemia and high-output heart failure, and the recipient because of hypervolemia. Prematurity is common in TTTS, attributable to the cumulative effects of twin pregnancy, polyhydramnios, fetal intervention, and, in some cases, rescue delivery for fetal deterioration.

Knowledge Gaps: Exact correlation between placental characteristics and susceptibility for severe chronic TTTS in monochorionic twin pregnancies remains unclear. Further studies are needed to determine the anatomical, biochemical and molecular mechanisms underlying the development of TTTS in its typical and atypical forms. Refined antenatal choriovascular imaging methods and identification of biochemical and other biomarkers predictive of prognosis may allow improved management of TTTS pregnancies.

The Laser-Treated Monochorionic Twin Placenta (Synonyms: Fetoscopic Laser Occlusion of Communicating [or Chorangiopagus] Vessels [Floc], Laser Ablation, Laser [Photo]Coagulation)

Definition: Placenta treated with fetoscopic laser coagulation of intertwin vascular anastomoses in monochorionic pregnancy complicated by twin-to-twin transfusion syndrome (TTTS).

Clinical Context: Fetoscopic laser occlusion of placental anastomoses is currently the treatment of choice for advanced or progressive TTTS diagnosed before 26 weeks' gestation[31]. This procedure interrupts the

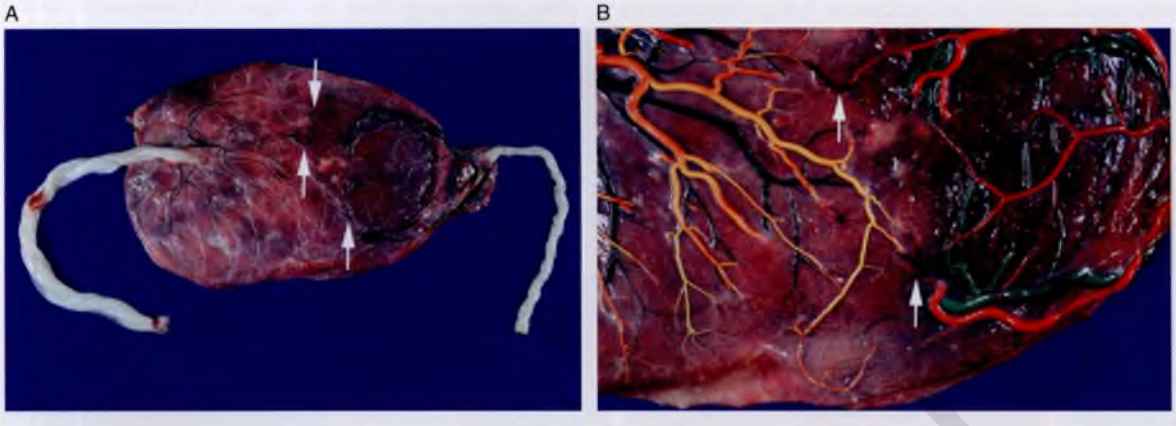

Figure 25.7 TTTS placenta following recent laser coagulation of communicating vessels. (a) TTTS placenta showing velamentous cord insertion, thin cord, and small territory of donor twin (right), and edematous cord of recipient twin (left). Hemorrhagic, thrombosed communicating vessels are noted along the equator (arrows). (b) Same placenta following vascular injection showing abrupt interruption of dye filling of coagulated communicating vessels (arrows). Color code. Left (recipient) twin: artery yellow, vein black; right (donor) twin: artery red, vein green. The intertwin membrane has been removed prior to injection.

hemodynamic imbalance that defines the syndrome by "dichorionizing" the initially monochorionic placenta. This prevents shifting of blood volume between twins and, importantly, also ensures functional separation of both circulations in the event of one twin's demise. Survival rates of at least one twin following laser coagulation range between 65 and 85 percent, while survival rates of both twins range between 45 and 70 percent[53,54].

Technical approaches for laser ablation include photocoagulation of all vessels or anastomoses crossing the intertwin membrane, coagulation of the suspected causative AV anastomosis only, or coagulation of the entire vascular equator (anastomoses as well as intervening parenchyma) (the so-called Solomon technique)[38]. Alternative, nonspecific management options for severe chronic TTTS include: repetitive amniodrainage (amnioreduction) of the polyhydramniotic sac of the recipient twin (65 percent survival of at least one twin); intertwin amniotic septostomy; and expectant management. Depending on gestational age at diagnosis and fetal status, selective cord coagulation and preterm delivery may be considered.

Gross Features: Pathologic findings following laser coagulation of communicating vessels depend on the treatment approach and on the time interval between intervention and delivery. Placentas treated by selective laser coagulation of the communicating vessels display subtle lesions limited to chorionic vessels. When examined within one month after selective laser coagulation, areas of laser impact are usually identifiable as hemorrhagic, clotted vessels along the vascular equator (Figure 25.7a)[38,55]. Vascular injection with air, saline or dye will expose abrupt filling interruption of the impacted chorionic vessels (Figure 25.7b)[38,55]. These coagulated vessels are typically situated along the recipient side of the intertwin membrane, as the fetoscope is usually inserted through the polyhydramniotic sac of the recipient. Placentas examined after more prolonged time intervals frequently display regional or complete absence of intertwin anastomoses, often associated with subchorionic fibrin deposition (Figure 25.8)[38,55]. The Solomon technique results in extensive, even full-thickness placental necrosis along the vascular equator[38].

Microscopic Features: Laser-treated vessels show varying degrees of necrosis associated with focal hemorrhage, aggregates of avascular villi, and focal intervillous hemorrhage and fibrin deposition in the underlying parenchyma (Figure 25.9). Placentas treated with the more aggressive Solomon procedure display extensive placental necrosis and infarction.

Ancillary Diagnostic Testing: Vascular injection studies may provide important feedback to the interventional team with respect to the efficiency of the coagulation procedure and, sometimes, may help explain an atypical post-surgical outcome. Of note, anastomoses that become evident after *ex vivo* injection may not have functioned as patent vessels *in vivo*,

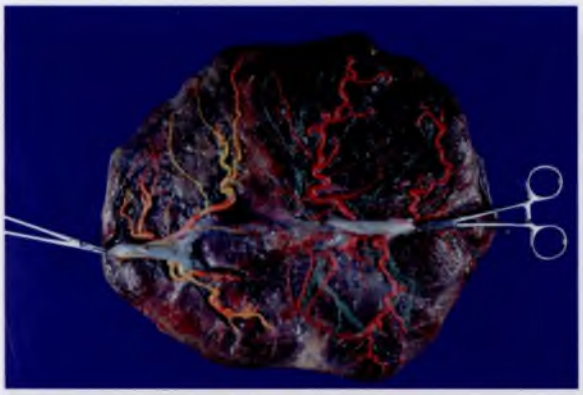

Figure 25.8 TTTS placenta following remote laser coagulation of communicating vessels. Placenta examined several months after laser coagulation showing absence of residual vascular communications, associated with fibrin deposition along the prior vascular equator. Color code. Left (previous donor) twin: artery yellow, vein black; right (previous recipient) twin: artery red, vein green. The intertwin membrane has been removed prior to injection.

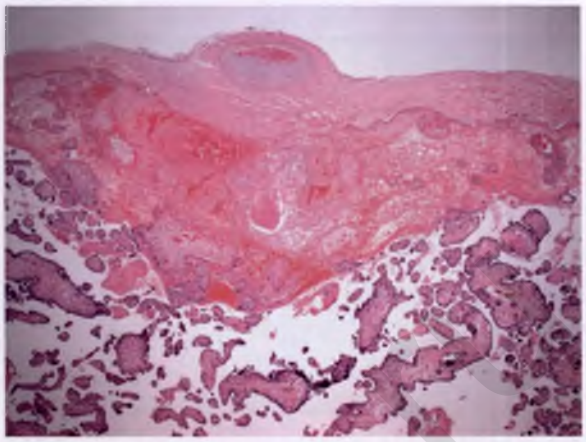

Figure 25.9 Histology of coagulated chorionic vessels. Chorionic vessel showing coagulative necrosis, associated with subchorionic fibrin deposition and necrotic and avascular villi. The lack of dye filling is consistent with effective vessel coagulation.

as vascular injection is carried out with supraphysiologic pressures. As in any twin pregnancy, zygosity studies may be indicated.

Prognostic Implications: Patent intertwin vascular communications, usually small and peripherally located, may remain present in up to 33 percent of cases treated by the selective approach[38,55–57]. Depending on their number, size, type, and direction, residual intertwin anastomoses may be associated with persistent TTTS, recurrent TTTS (5–14 percent), reversal of TTTS whereby donor becomes recipient and vice versa, twin anemia-polycythemia syndrome (TAPS, 5–13 percent), or intrauterine demise of one or both twins[58]. The incidence of TAPS and recurrent TTTS may be reduced by the Solomon technique[59].

Knowledge Gaps: The exact physical, biochemical, and/or hormonal mechanisms whereby the various laser coagulation approaches modulate the syndrome and outcome remain unclear. Biomarkers of fetal status and severity of TTTS are needed to guide the timing and technical approach of any surgical intervention.

Twin-Anemia-Polycythemia Sequence (TAPS)

Definition: A recently described form of chronic twin-to-twin transfusion in monochorionic pregnancies, characterized by the presence of a large intertwin difference in hemoglobin and reticulocyte levels in the absence of oligohydramnios/polyhydramnios.

Clinical Context: TAPS is a form of chronic and slow intertwin blood transfusion that results in large intertwin hemoglobin differences without associated twin oligohydramnios-polyhydramnios sequence (TOPS)[58,60]. The absence of a severe amniotic fluid discordance is essential for diagnosis of TAPS, since the presence of TOPS is diagnostic of TTTS. TAPS may occur spontaneously ("spontaneous" TAPS; estimated incidence 3–6 percent of monochorionic twin pregnancies) or iatrogenically following laser treatment for TTTS ("post-laser" TAPS)[42]. Spontaneous TAPS typically presents after 26 weeks' gestation. Post-laser TAPS occurs in up to 16 percent of TTTS pregnancies after incomplete laser treatment and usually presents within 1 to 5 weeks after the laser surgery[60]. Interestingly, usually the former recipient becomes anemic, whereas the former donor becomes polycythemic[56,58].

TAPS can be diagnosed antenatally or postnatally. The antenatal diagnosis is based on Doppler ultrasound criteria and depends on the presence of an intertwin difference in middle cerebral artery peak systolic velocity (MCA-PSV)[61]. Postnatal TAPS diagnosis is suspected in the presence of a large intertwin hemoglobin difference (>8 g/dL). Two additional criteria are proposed to differentiate between TAPS and acute peripartum TTTS, a clinically distinct condition that may also lead to significant intertwin hemoglobin differences at birth. The first criterion is

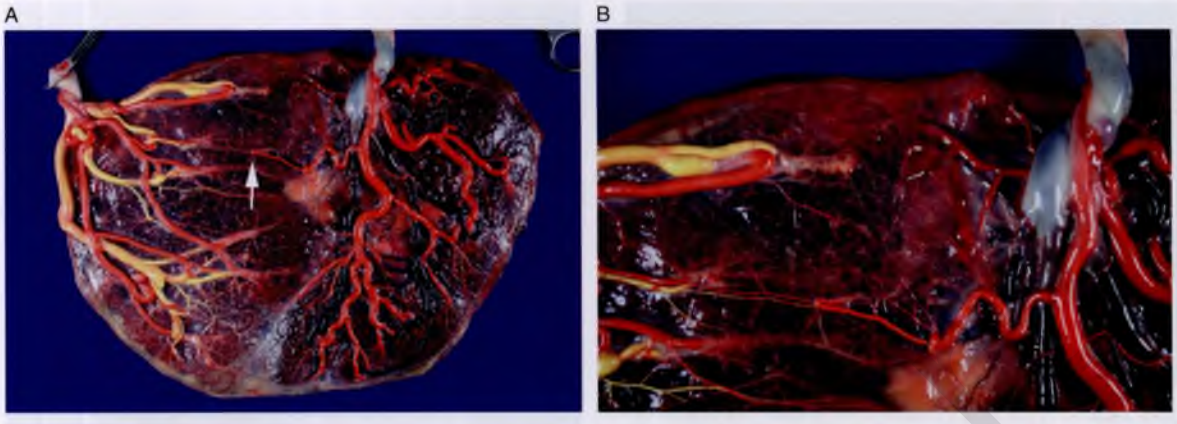

Figure 25.10 Placenta of twin pregnancy complicated by TAPS: fetal side. (a) TAPS placenta showing characteristically small-sized AA anastomosis (arrow) and paucity of AV anastomoses. Color code. Left (anemic) twin: artery red, vein yellow; right (polycythemic) twin: artery red, vein black. The intertwin membrane has been removed prior to injection. (b) Closer view of the minuscule AA anastomosis.

an increased reticulocyte count in the donor (as evidence of chronic anemia), expressed as ratio of donor reticulocyte count over recipient reticulocyte count (proposed cut-off value for TAPS: >1.7)[62]. The second criterion is the presence of (residual) intertwin anastomoses (diameter < 1 mm), usually detected by vascular injection[42]. The value of more recent criteria proposed for postnatal diagnosis of TAPS, including color difference of the maternal side of the placenta (pallor of anemic donor side; plethoric appearance of the recipient side)[63–65] and prolonged persistence of postnatal erythroblastosis[66], remains to be established.

There is no consensus on optimal management of TAPS. Current options include expectant management, induction of labor, intrauterine transfusion in the donor with or without partial exchange transfusion in the recipient, selective feticide, and (repeat) fetoscopic laser surgery[60]. Laser coagulation is the only causal treatment but technically challenging in view of the small size of the communicating vessels and the absence of polyhydramnios.

Proposed Pathogenesis: The pathogenesis of TAPS has been linked to its unique placental angioarchitecture, characterized by the presence of only a few, small anastomoses[67]. These few minuscule intertwin anastomoses are believed to allow chronic and slow transfusion of blood from donor to recipient twin. This gradual net transfusion results in highly discordant hemoglobin levels, causing the donor twin to become anemic and the recipient twin to become polycythemic. The chronic, gradual character of intertwin blood transfusion in TAPS is believed to allow time for hemodynamic compensatory mechanisms in the absence of hormonal imbalance, thus preventing the development of oligohydramnios and polyhydramnios in donor and recipient, respectively[67,68]. In contrast, development of TTTS has been attributed to larger, more acute intertwin transfusion and secondary unbalanced hormonal regulation.

Gross Features: The typical angioarchitectural pattern associated with TAPS consists of sparse (3–4 per placenta, on average) and small-sized (diameter < 1 mm) AV anastomoses[42,64] (Figure 25.10a). AA anastomoses occur in only 10–20 percent of TAPS placentas and, when present, are smaller (diameter < 1 mm) than in TTTS placentas or in placentas of uncomplicated monochorionic twin pregnancies [42,69] (Figure 25.10b). VV anastomoses are even less frequent[42]. The reported number of anastomoses in spontaneous TAPS placentas is slightly higher than in post-laser TAPS placentas (4 versus 2, on average). In both conditions, anastomoses are more frequently located along the periphery of the placenta[70]. Some TAPS placentas display a distinct color difference on the maternal side, with pale parenchyma on the side of the anemic twin and dark red parenchyma on the side of the polycythemic twin[63–65] (Figure 25.11). Corresponding differences in placental echogenicity can be observed by antenatal ultrasound examination[63,71]. The specificity of this finding as a marker for TAPS remains unclear.

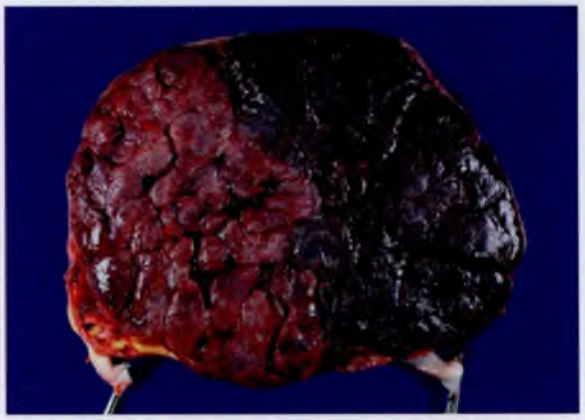

Figure 25.11 Placenta of twin pregnancy complicated by TAPS: maternal side. Basal plate of the same placenta as shown in Figure 25.10, showing parenchymal pallor of the anemic twin and parenchymal congestion of the polycythemic twin.

Microscopic Features: The TAPS placenta has no specific histopathologic features. The fetal circulations of both twins may show differences in congestion and numbers of circulating erythroid precursors (evidence of chronic twin-to-twin transfusion).

Ancillary Diagnostic Testing: As in every twin pregnancy, zygosity studies may be indicated. Hematologic analyses may reveal intertwin differences in hemoglobin/hematocrit and erythroid precursors, indicative of acute or chronic twin-to-twin transfusion. Vascular injection studies may aid in visualization of the often-minuscule intertwin anastomoses in TAPS placentas.

Prognostic Implications: Concrete data on perinatal and long-term morbidity in TAPS twins are scarce. Some studies have suggested higher rates of perinatal complications in TAPS, with neonatal outcomes ranging from isolated large intertwin hemoglobin differences to severe neonatal morbidity, including cerebral injury and neonatal death[72]. TAPS donors and recipients may require blood or partial exchange transfusions, respectively. TAPS recipients are at risk for polycythemia-hyperviscosity syndrome, with secondary ischemic skin and limb necrosis[58]. Other reported abnormal findings in TAPS twins include thrombocytopenia (in recipients), hypoalbuminemia and hypoproteinemia (in donors), renal dysfunction (in donors), and cerebral injury (in donors and recipients)[60]. The long-term neurodevelopmental outcome of TAPS twins remains unknown[60].

Knowledge Gaps: TAPS is a relatively recently described identity; further large-scale studies are required to determine optimal diagnostic criteria, natural history, optimal management strategies, and long-term outcome of TAPS survivors. From a pathologic perspective, further unbiased investigation in larger cohorts is required to determine the exact significance, sensitivity and specificity of placental findings in TAPS. The relationship between TAPS and TTTS, and the mechanisms underlying or preventing putative transition from TAPS to TTTS remain unclear.

Twin Reversed Arterial Perfusion (TRAP) Sequence (Acardiac Twinning) (Synonyms: Acardius, Chorangiopagus Parasiticus Twin)

Definition: A severe form of chronic twin-to-twin transfusion in monochorionic twin pregnancies, characterized by lack of cardiac development and/or function and usually striking malformations of the acardiac twin. In this typical constellation of twin and placental anomalies, the twin with circulatory failure (the acardiac twin) is perfused in a paradoxical retrograde fashion by a structurally normal "pump" twin through what is characteristically a single superficial artery-to-artery anastomosis, hence the name "reversed arterial perfusion."

Clinical Context: The TRAP sequence is rare, with an estimated incidence of about 1 in 35,000 pregnancies[73] or 1 percent of monochorionic twin pregnancies[53,74–76]. The acardiac twin displays a spectrum of anomalies, most typically underdevelopment or absence of upper body and head, relative preservation of the lower extremities, marked edema, and absence of identifiable cardiac pulsation. A two-vessel cord is present in two-thirds of cases[77]. The pump twin may develop high-output cardiac failure, especially when the weight of the acardiac twin is >50 percent that of the pump twin. The optimal management strategy for pregnancies complicated by the TRAP sequence remains poorly defined. Expectant management is associated with 35–50 percent mortality in the pump twin. Fetoscopic laser coagulation of the umbilical cord and/or placental anastomoses or radiofrequency

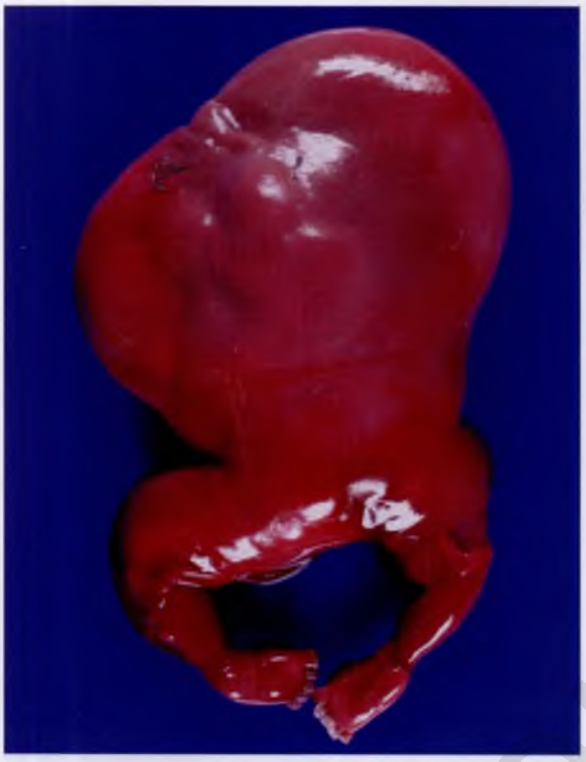

Figure 25.12 Acardius acephalus. Acardiac twin showing well-developed lower extremities, but absence of upper extremities and head.

ablation of the lower abdominal region of the acardiac twin, targeting the intra-abdominal vessels, results in 70–90 percent survival of the pump twin[78,79].

Proposed Pathogenesis: Although the exact pathogenesis of acardiac twinning remains controversial, general consensus is that two conditions need to be fulfilled for its development[80,81]. First, one of the twins in a monochorionic pregnancy must have a circulatory failure/nonfunctional heart during the first trimester of pregnancy (between 8 and 12 weeks' gestation). Second, the placenta must have a specific angioarchitecture, defined by at least one direct artery-to-artery (and usually also vein-to-vein) intertwin anastomosis, in order to support continued development of the acardiac twin.

As a result, the acardiac twin loses its vascular connections to the placenta, resulting in a bypass of placental villous parenchyma, and depends on the co-twin ("donor" or "pump" twin) for all somatic blood supply. The pump twin shunts part of its cardiac output toward the parasitic acardiac co-twin through retrograde flow into its umbilical artery or arteries via the intertwin AA anastomoses, resulting in reversed circulation for the acardiac twin. Because the blood flows in a retrograde fashion through the umbilical artery (a branch of the internal iliac artery) or, in some cases, directly into the abdominal aorta, the lower body of the acardiac twin is supplied preferentially with blood that is already partially deoxygenated upon entry into the acardiac somatic circulation. This results in relatively better development of the lower body in most acardiac twins.

Gross Features: The acardiac twin shows a wide range of significant structural anomalies, usually featuring relative preservation of the lower limbs associated with underdevelopment of upper body and head (with exception of acardius amorphus and acardius acormus). The following acardiac phenotypes are recognized: acardius acephalus (60–75 percent, well-developed pelvis and lower limbs, but no cranial or thoracic development and often no upper limbs) (Figure 25.12); acardius anceps (15 percent, well-developed body and extremities, but only partial cranial development); acardius amorphus (least differentiated, amorphous tissue mass without recognizable features; rare) and acardius acormus (only cephalic development; very rare).

The size of the acardiac twin varies greatly from an incidental structure to a large mass more than twice the size of the pump twin[82]. In addition to subcutaneous edema, absent craniofacial structures, an incomplete spine and hypoplastic thorax, malformations in acardiac twins include intestinal atresia, imperforate anus, and renal or hepatic agenesis. The heart may be completely absent (holoacardius), rudimentary (pseudoacardius), or relatively well-formed; <20 percent have some identifiable (nonfunctional) cardiac tissue[77]. Lung development is variable. The pump twin is usually structurally normal. However, associated anomalies have been reported, including prune belly, renal agenesis and dysplasia, renal tubular dysgenesis, anal atresia, gastroschisis, and pulmonary artery calcification[83,84].

The placenta in TRAP pregnancies may be diamniotic-monochorionic or monoamniotic-monochorionic. The umbilical cords of pump and acardiac twin are usually inserted close to one another, or may share a common insertion site. The cords have direct vascular large AA (and often VV) anastomoses, which allow reversed flow in the participating umbilical artery of

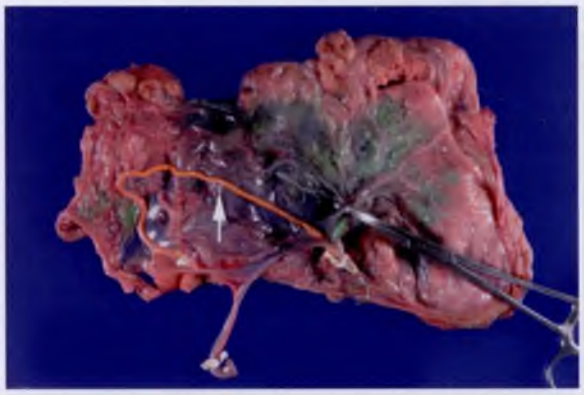

Figure 25.13 Placenta of twin pregnancy complicated by TRAP sequence. TRAP placenta showing direct AA anastomosis between both umbilical cords (arrow), bypassing the placental parenchyma.

the acardiac twin (Figure 25.13). Acardiac twin pregnancies managed by fetoscopic laser coagulation or radiofrequency ablation display evidence of surgical intervention, focused on the umbilical vessels, abdominal cord insertion site, or lower abdomen of the acardiac twin.

Microscopic Features: The histopathology of the acardiac twin is highly variable. In more developed types (acardius acephalus and acardius anceps), examination may reveal partial cardiac and pulmonary development.

Ancillary Diagnostic Testing: Placental vascular injection studies may facilitate visualization of the characteristic angioarchitecture, i.e., the presence of direct AA and usually also VV anastomoses connecting both umbilical cords. Genetic studies may reveal chromosomal anomalies in the acardiac twin.

Prognostic Implications: The malformations of the acardiac twin are uniformly lethal postnatally as the acardiac fetus is hemodynamically dependent on the pump twin. The growth and existence of the acardiac twin threatens the survival of the pump twin by increasing the risk of high output congestive cardiac failure, polyhydramnios, and preterm delivery. Perinatal mortality rates for the pump twin range between 35 and 55 percent [76,77,85]. Poor prognostic factors for the pump twin include acardiac-to-pump twin fetal weight ratio >70 percent, pump twin congestive heart failure, polyhydramnios, certain morphologic features in the acardiac twin such as anceps acardia and presence of arms, and delivery before 32 weeks' gestation[76,77]. Surgical management significantly improves outcome, with survival rates above 70 percent[78,79].

Knowledge Gaps: The exact pathogenesis of the TRAP sequence remains poorly understood. In specific, it is unclear whether the primary event is abnormal cardiac embryogenesis or aberrant chorionic vascular development.

Fetal Growth Discordance in Monochorionic Twins (Synonyms: [Severe] Growth Discrepancy, [Severe] Growth Restriction)

Definition: Variably defined as more than 20–25 percent discordance between estimated fetal weights or birth weights of monochorionic twin pregnancies not complicated by TTTS. Includes or implies severe intrauterine growth restriction (IUGR) of one twin.

Clinical Context: Selective or isolated severe growth discordance is more common in monochorionic twins (estimated incidence 12–36 percent) than in dichorionic twins (estimated incidence 7–18 percent)[16]. The degree of discordance, expressed as a percentage, is calculated as the difference between the estimated fetal or birth weight of the larger twin and that of the smaller twin, multiplied by 100 and divided by the weight of the larger twin. The optimal management of growth-discordant monochorionic pregnancies is not well established. Options include selective reduction of the smaller twin in the previable period or close fetal monitoring with umbilical artery Doppler evaluation and possible elective preterm delivery at later gestational ages.

Proposed Pathogenesis: Monochorionic twins are virtually always monozygotic and thus have in theory the same genetic growth potential. The most important determinant of selective (non-TTTS-related) growth discordance in monochorionic twin pregnancies is unequal placental sharing (usually associated with abnormal cord insertion of one or both twins)[44,86–88]. Recent studies suggest decreased angiogenic activity in monochorionic twin pregnancies associated with selective growth restriction (and TTTS), presumptively reflective of abnormal placentation[89].

Gross Features: Placentas of monochorionic twin pregnancies complicated by selective growth

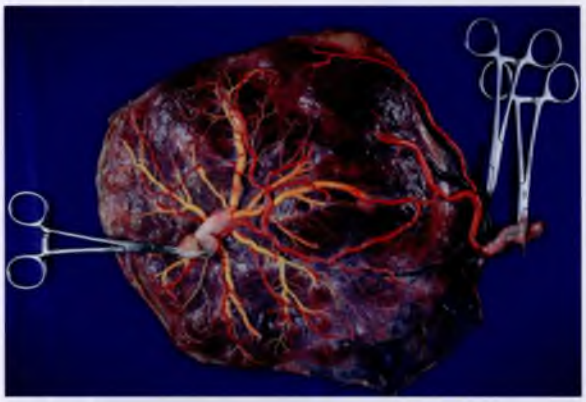

Figure 25.14 Placenta of twin pregnancy complicated by severe growth discordance. The smaller (right-sided) twin has a velamentous cord insertion and smaller placental share of this diamniotic-monochorionic placenta. Color code. Left twin: artery red, vein yellow; right twin: artery red, vein black. The intertwin membrane has been removed prior to injection.

discordance have a higher frequency of uneven placental sharing and/or peripheral (marginal or velamentous) cord insertion of at least one twin (Figure 25.14) than growth-concordant twin placentas[86]. One study suggests that placental characteristics may be different for pregnancies with early discordant growth (diagnosed at ≤ 20 weeks' gestation) compared with those where discordant growth is diagnosed later in pregnancy[90]. Twin pregnancies with early-onset discordant growth tend to have unequally shared placenta compartments with large anastomoses (20 percent mortality). On the other hand, pregnancies with progressive growth discordance developing after 26 weeks' gestation tend to have more equally shared placental compartments and with smaller anastomoses (almost 0 percent mortality, although risk of TAPS may be increased)[90].

Microscopic Features: The placenta may demonstrate discordant villous maturation between twins: villous maturation tends to be accelerated in the territory of the smaller twin, with peripheral cord insertion and/or smaller placental share.

Ancillary Diagnostic Testing: Not routinely needed for placental diagnosis. As in all twin pregnancies, zygosity studies are indicated. Vascular injection studies are optional.

Prognostic Implications: Twin growth discordance is associated with excess perinatal morbidity and mortality[88]. The outcome is determined by the onset and severity of discordance, degree of growth restriction, interval growth, and amniotic fluid volume of the smaller twin. Both twins are at increased risk for intrauterine demise.

Knowledge Gaps: There is a lack of reliable methods, such as antenatal imaging techniques and biomarkers, to estimate fetal prognosis and to assist in management decisions (e.g. expectant management versus elective delivery).

MONOCHORIONIC MONOAMNIOTIC TWINNING AND ASSOCIATED COMPLICATIONS

General Pathologies of Monoamniotic Placentation

Definition: Twin or multiple pregnancy characterized by a monoamniotic type of placentation, in which the twins share a single placenta and a single amniotic sac, in the absence of a dividing membrane.

Clinical Context: Monoamniotic-monochorionic pregnancies represent the least common type of twin placentation, accounting for less than 2 percent of all twin gestations and about 5–15 percent of all monozygotic twins. Reported mortality rates for monoamniotic twins range between 10 and 40 percent[26]. Umbilical cord entanglement is a specific risk of monoamniotic twin pregnancies (and, parenthetically, of diamniotic pregnancies with disrupted septum following spontaneous or iatrogenic septostomy). Mortality risk of cord entanglement is highest at less than 24 weeks' gestation, when fetuses are small and mobile in the single amniotic sac.

Like all twin pregnancies, monoamniotic-monochorionic twins are at increased risk for growth restriction and congenital anomalies, and nearly 100 percent of monoamniotic surviving twins are delivered preterm. The reported incidence of TTTS in monoamniotic twins is lower than that in diamniotic twins (3–10 percent versus 9–15 percent)[38], which has been attributed to the virtually ubiquitous presence of large-sized compensatory AA anastomoses and shorter inter-cord distance in monoamniotic placentas[91]. In monoamniotic twin pregnancies, the diagnosis of TTTS is not based on the standard ultrasound criteria of oligohydramnios/

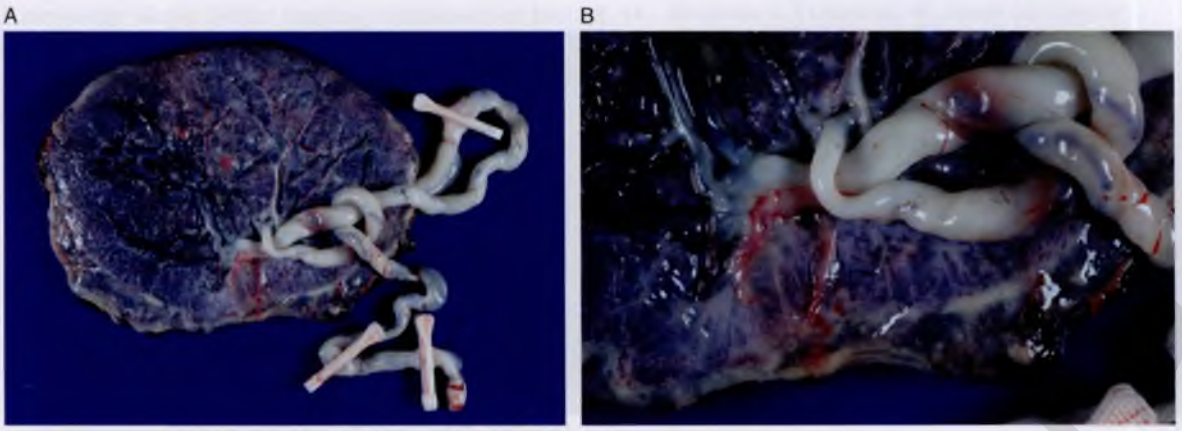

Figure 25.15 Monoamniotic twin placenta with cord entanglement (a) Monoamniotic twin placenta showing closely inserted, loosely entangled umbilical cords. (b) Closer view of the cord insertion sites showing marked thinning of one cord.

polyhydramnios, as the absence of an inter-twin septum precludes the development of inter-twin imbalances in amnion volume. Instead, the diagnosis of TTTS in monoamniotic twin pregnancies is based on other prenatal ultrasound criteria, such as polyhydramnios, discordance in bladder size, and abnormal Doppler patterns in either twin[92].

TAPS is extremely rare in monoamniotic twins. In one reported case of TAPS occurring in monoamniotic twins, large anastomoses were absent, and only very small AV anastomoses were present[93]. About half of TRAP pregnancies occur with monoamniotic placentas; the outcomes and phenotypes of monoamniotic acardiac twins are similar to those of diamniotic-monochorionic acardiac twin pregnancies (described above).

The incidence of conjoined or incompletely separated twinning is estimated at 1 in 100,000 to 1 in 250,000 live births, but shows striking regional variation. Conjoined twins are categorized based on the most prominent site of fusion. The majority of conjoined twins are fused at the chest (thoracopagus, 70 percent). Omphalopagus, pygopagus, ischiopagus and craniopagus indicate fusion at abdomen, perineum, pelvis/lower body, and head, respectively. Surgical success and long term outcomes are mainly determined by the degree of cardiovascular anomalies, which range from a single heart with isomerism, to two hearts with abnormal laterality, to complex compound hearts with fusion of venous sinuses/atria/atria and ventricles[94].

Proposed Pathogenesis: Monoamniotic-monochorionic placentation occurs when the inner cell mass of the blastocyst divides relatively late (8–12 days post-fertilization), resulting in two fetuses and a single placenta (one chorion and one amnion) (division at earlier time points results in dichorionic or diamniotic-monochorionic placentation). The mechanisms underlying the formation of conjoined twins are unclear, but may involve incomplete splitting of the embryonic disc at 13–16 days post-fertilization ("fission" theory) or partial secondary fusion of two previously separate single-ovum embryonic discs ("fusion" theory)[95].

Gross Features: The monoamniotic placental membranes form a single sac without dividing intertwin membrane. The umbilical cords of monoamniotic placentas typically insert very close to each other on the chorionic plate (Figures 25.15–16) and are almost always connected by large-caliber superficial vascular anastomoses (usually AA anastomoses)[91] (Figure 25.16). The cords may be fused or furcate. The cords may be entangled with each other, often in complex patterns, (Figure 25.15) and may display gross evidence of vascular compromise such as cord narrowing, grooving, edema or vascular thrombosis. Abnormal peripheral cord insertion and single umbilical artery (two-vessel cord) are common.

Placentas of conjoined twins are almost always monoamniotic-monochorionic. The structure of the umbilical cords varies widely, with either a single fused umbilical cord originating from the placenta (with 3 to 8 umbilical vessels) or two separate cords

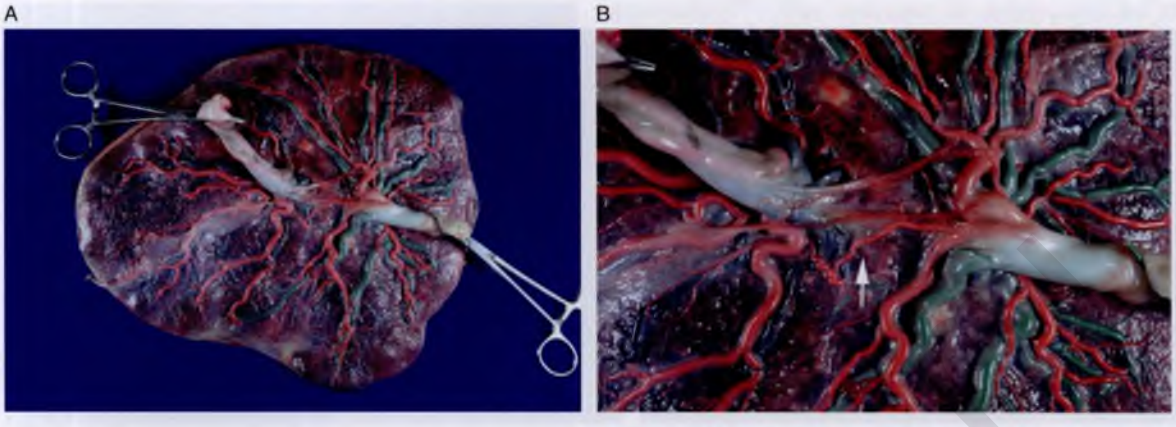

Figure 25.16 Monoamniotic twin placenta. (a) Overview showing the intimate connections between the two vascular beds. Due to the presence of AA and VV anastomoses, the vascular beds of both twins share the same color. Color code: Artery red, vein green. (b) Closer view showing the closely inserted cords, directly connected by AA anastomosis (arrow).

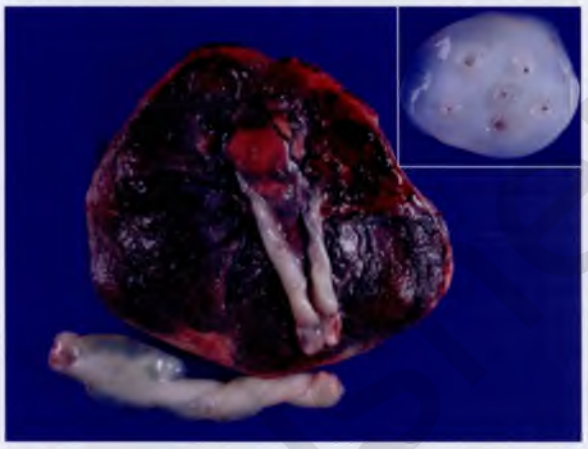

Figure 25.17 Monoamniotic twin placenta in conjoined twinning. Monoamniotic twin placenta showing partial fusion of umbilical cords (bottom segment). Inset shows a cross-section of a fused cord, demonstrating 6 umbilical vessels (2 veins, 4 arteries).

(Figure 25.17). Rare cases of conjoined twins with diamniotic-monochorionic placentas have been reported, presumptively explained by early duplication of the primitive streak during gastrulation[96].

Microscopic Features: Abnormal (marginal, velamentous) cord insertions and cord entanglements are associated with an increased incidence of fetal vascular malperfusion (i.e., evidence of chronic or intermittent fetal vascular obstruction), such as chorionic or stem villus thrombosis, avascular villi and villous stromal-vascular karyorrhexis.

Ancillary Diagnostic Testing: Not routinely needed for placental diagnosis. Vascular injection studies are optional.

Prognostic Implications: Most recent studies suggest a better perinatal outcome for monoamniotic pregnancies than previously reported, with survival rates up to 88 percent[24]. Adverse perinatal outcomes in monoamniotic twins are attributable primarily to prematurity and umbilical cord entanglement or compression, and, to a lesser extent, to discordant major congenital anomalies, growth restriction, TTTS, and twin reversed arterial perfusion (TRAP, acardiac twinning)[97]. Monoamniotic twinning is associated with increased fetal anomaly rates (20–25 percent), even when monoamniotic conjoined twins are excluded[83,98]. Monoamniotic twins are at increased risk of unexpected and usually dual intrauterine demise, believed to be triggered by cord compression followed by acute feto-fetal transfusion through the large anastomoses[44].

Conjoined twinning is associated with complications related to abnormal/fused organs and tissues and the subsequent superimposed effects of abnormal hemodynamics[83]. Other congenital anomalies not directly linked to organ fusion are present in about 80 percent of conjoined twins[99]. Cardiovascular anomalies represent the main limiting factors influencing separation approaches and long term survival. Overall intrauterine mortality of conjoined twins is estimated to be 47 percent[100].

Knowledge Gaps: Better imaging techniques or biomarkers are required to estimate the presence and impact of cord entanglement. The mechanisms underlying the relatively high incidence of malformations and disruptions in monoamniotic twins remain unclear.

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Chapter 26

Dichorionic and Higher Order Multiple Gestations

Monique E. De Paepe

The Dichorionic Twin Placenta

Definition: Twin placenta characterized by the presence of a chorion (and amnion) for each twin.

Clinical context: About 75–80 percent of twins in the United States have a dichorionic form of placentation. Twins with dichorionic placentas may be either dizygotic (derived from two separate fertilized ova; representing 70 to 85 percent of all spontaneous dichorionic gestations) or monozygotic (derived from a single fertilized ovum; representing 15 to 30 percent of all spontaneous dichorionic gestations). In the United States, the incidence of twin births has increased almost twofold between 1971 and 2009[1,2], mainly resulting from increased use of assisted reproduction associated with increasing maternal age at conception[2]. The rates of dizygotic twinning show large regional differences, from 6 per 1,000 births in Asia to 40 per 1,000 births in Sub-Saharan Africa[3]. In contrast, monozygotic twinning occurs at a constant rate of about 3 to 4 per 1,000 births worldwide[4].

Proposed Pathogenesis: The basic mechanism underlying spontaneous dizygotic twinning is the concurrent release and fertilization of two or more oocytes during the same menstrual cycle (polyovulation). Mothers of dizygotic twins have a predisposition to multiple ovulation events due to dysregulation of single dominant follicle selection. Genetic mapping studies are beginning to unravel the genes and pathways contributing to dizygotic twinning. Associations between dizygotic twinning and variants in factors controlling ovarian folliculogenesis and ovulation have been reported, such as growth differentiation factor 9 (*GDF9*)[5,6], follicle-stimulating hormone (FSH) B (*FSHB*), and *SMAD3*, the latter product of which plays a major role in gonadal responsiveness to FSH[7]. However, these rare variants only account for a small portion of the genetic contribution to twinning. Dizygotic twins (virtually) always have dichorionic (diamniotic-dichorionic) placentas, as each zygote develops its own amnion, chorion, and placental circulations. For monozygotic twins, the placentation type correlates with the timing of zygotic division: early division results in a dichorionic twin placenta, whereas later division leads to monochorionicity (see Chapter 25). Unlike dizygotic twinning, monozygotic twinning is usually a sporadic, nonhereditary event, although rare familial clustering has been described.

Gross Features: Dichorionic twin placentas may be separate or fused, in roughly equal proportions. Close implantation of the blastocysts results in fusion of the placentas and formation of an apparently single disc with dividing septum and separate fetoplacental circulations (Figure 26.1a). The intertwin membrane of fused dichorionic placentas is relatively thick and opaque due to the presence of two fused chorions between the two amniotic layers. The fused chorionic tissue is continuous with the chorion of the underlying placenta and forms a ridge along the base of the intertwin membrane (Figure 26.1b), corresponding to the sonographic "twin peak" or "lambda" sign. In dichorionic placentas, the location of the septum corresponds to the fused borders of the twin placentas and thus defines the vascular equator of the two placentas. In virtually all cases, fused diamniotic-dichorionic twin placentas have separate chorionic vascular beds. Exceedingly rare exceptions have been described where fetal chorionic vessels cross the area of fusion[8]; the existence of such small anastomoses may explain the rare finding of blood group chimerism in dizygotic twins of opposite sex[9]. Reference values for combined weights of twin placentas have been established[10,11].

Microscopic Features: Chorionicity is confirmed by study of intertwin membrane layers in sections of the rolled intertwin membrane (Figure 26.2a) and/or "T-zone," where the membrane meets the chorionic

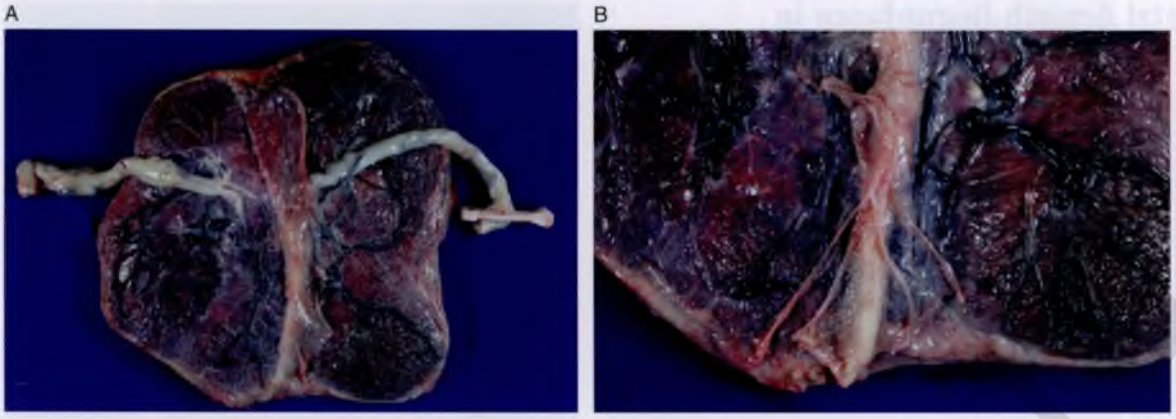

Figure 26.1 Diamniotic-dichorionic twin placenta (macroscopy). (a) Overview of fused dichorionic twin placenta showing prominent dividing septum and separate vascular beds. (b) Closer view of dividing septum showing the 4 layers of the intertwin membrane and septal ridge formed by protruding chorions.

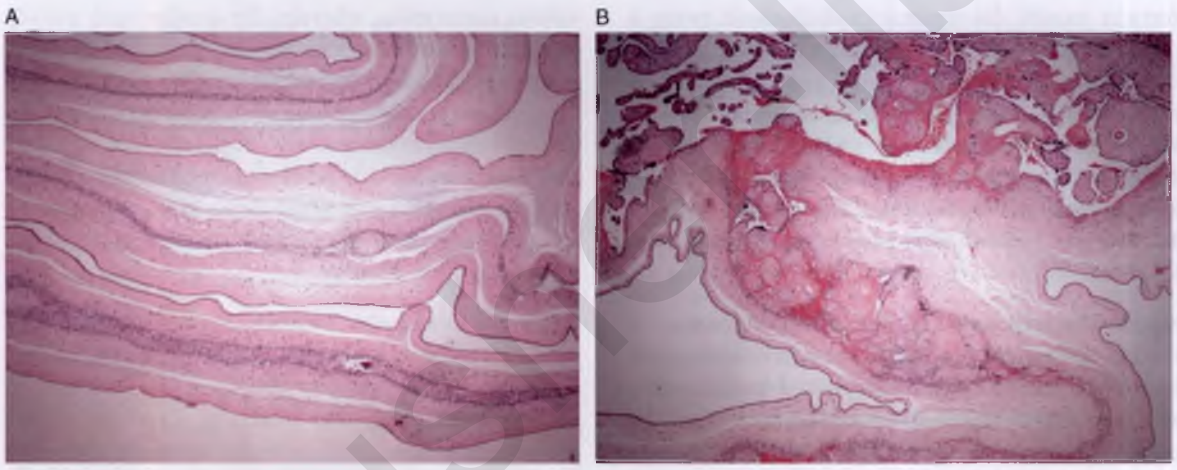

Figure 26.2 Intertwin membrane of dichorionic twin placenta (microscopy). (a) Intertwin membrane of a diamniotic-dichorionic twin placenta showing one (fused) or two chorion layers surfaced by amnion. (b) View of the "T-section" of the septum, showing the junction between the intertwin membrane and chorionic plate. Extension of chorionic villi into the membrane corresponds to the septal ridge.

plate (Figure 26.2b). The intertwin membrane of the diamniotic-dichorionic twin placenta is composed of two amnion layers separated by a fused layer of two chorions. Parenchymal sections may show discordant histologic findings in twin gestations, with disparate growth and/or outcome.

Ancillary Diagnostic Testing: Twins with dichorionic placentas, whether separate or fused, may be dizygotic or monozygotic. Sex discordance virtually always corresponds to dizygosity, although monozygotic twins of different sex have been described[12,13]. In same-sex dichorionic twins, further investigations are required to determine zygosity.

Prognostic Implications: Like all twin pregnancies, dichorionic pregnancies are at risk for premature delivery, discordant growth and preeclampsia. A recent meta-analysis compared the obstetric outcomes of dichorionic twin pregnancies after assisted reproductive technology (ART) to those conceived naturally[14]. The rates of placenta previa, preterm birth, very preterm birth, low birth weight and congenital malformations were higher in dichorionic twin pregnancies conceived after ART[14].

Knowledge Gaps: The exact prevalence and clinical relevance of intertwin anastomoses in fused dichorionic twin placentas remains unclear.

Fetal Growth Discordance in Dichorionic Twins (Twin Birth Weight Discordance, Discordant Severe Intrauterine Growth Restriction [IUGR])

Definition: Variably defined as more than 20–25 percent discordance between estimated fetal weights or birth weights of twins. Includes or implies severe intrauterine growth restriction (IUGR) of one twin. The degree of discordance, expressed as a percentage, is calculated as the difference between the estimated fetal or birth weight of the larger twin and that of the smaller twin multiplied by 100 and divided by the weight of the larger twin.

Clinical Context: The estimated incidence of severe intertwin growth discrepancy in dichorionic twins is 7–18 percent, which is parenthetically lower than in monochorionic twins. Although gestational age at birth and birth weight are the most important predictors of perinatal outcome, discordant growth is also independently associated with adverse outcome[15]. Precise, gestational age-specific cut-off values for critical inter-twin growth discordances have not been established[16].

Proposed Pathogenesis: Growth discordance may be linked to discordant placental characteristics, such as placental size, cord insertion type and location, placental implantation, uteroplacental perfusion, and/or placental parenchymal pathology[17]. In addition, the growth of dichorionic twins may be differentially influenced by nonplacental factors, such as genetic growth potential, structural or chromosomal fetal anomalies, or congenital infection[17].

Gross Features: In placentas with uneven placental sharing, the smaller share is virtually always associated with the smaller twin. Similarly, in placentas with discordant cord insertion types, the smaller twin usually has the abnormal (marginal or velamentous) cord insertion (Figure 26.3). Placental parenchymal lesions associated with maternal vascular malperfusion (e.g. infarcts, fibrin deposition, retroplacental hematoma), when present, are seen predominantly in the territory of the smaller twin.

Microscopic Features: The fused placenta of weight-discordant dichorionic twins may display discordant villous maturation, whereby the smaller twin usually exhibits features associated with maternal vascular malperfusion, often in association with smaller a placental share and/or extreme peripheral cord insertion. These features of the growth-restricted placental compartment may include accelerated villous maturation. infarcts, subchorionic fibrin deposition, retroplacental hematoma, perivillous fibrin deposition, and villitis of unknown etiology.

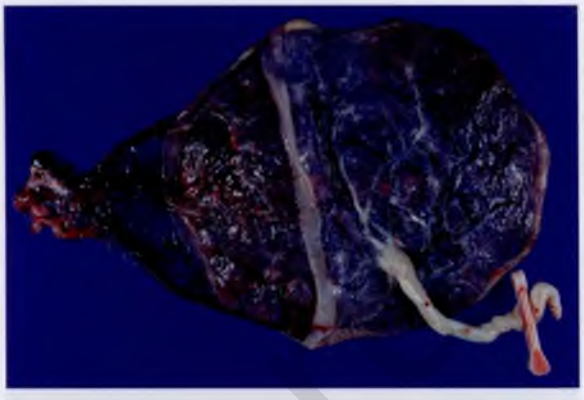

Figure 26.3 Dichorionic twin placentas with growth discordance. Dichorionic twin placentas showing discordance in size and with velamentous cord insertion in one twin.

Ancillary Diagnostic Testing: Appropriate ancillary studies may be indicated in cases involving discordant chromosomal anomalies, structural fetal anomalies, or suspected congenital infection. Zygosity studies are recommended, especially for same-sex dichorionic twins.

Prognostic Implications: Twin growth discordance is associated with excess perinatal morbidity and mortality with increasing levels of birth weight discrepancy, regardless of gestational age at delivery. Both smaller and larger twins are at increased risk for intrauterine death. A difference in estimated fetal weight >25 percent has been proposed as predictive of perinatal mortality after 26 weeks' gestation and may be used as indication for increased surveillance [18].

Knowledge Gaps: Clinically relevant and age-specific cut-off values for critical estimated fetal weight discordance have not been established. The long-term effects of severe twin growth discordance on growth, health and neurologic outcome remain to be determined.

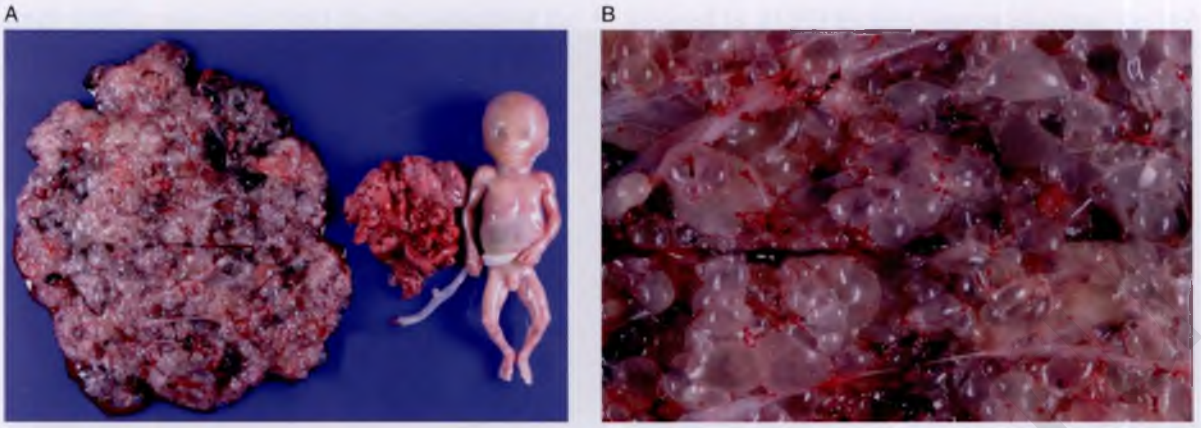

Figure 26.4 Complete hydatidiform mole with coexistent twin (macroscopy). (a) Dichorionic twin pregnancy composed of a typical molar component (left) and a normal fetus and placenta (right). (b) Closer view of the molar component, showing the grape-like cystic structures typical of a complete hydatidiform mole.

Complete Hydatidiform Mole with twin Placenta (Complete Hydatidiform Mole with Coexistent [Live or Viable] Fetus [CHM-CF])

Definition: A twin or multiple pregnancy characterized by the presence of a fetus with normal anatomy and karyotype in association with a hydatidiform molar component.

Clinical Context: The reported incidence of complete hydatidiform mole with coexistent live or viable fetus (CHM-CF) is between 1 in 22,000 and 1 in 100,000 pregnancies[19,20]. The diagnosis of CHM-CF is usually suspected by first trimester or early second trimester ultrasound scan, often in combination with an unusually high level of serum beta-HCG. The abnormal placenta has a characteristic "snow-storm" appearance, showing multiple sonographic lucencies sized 0.1 cm to 3 cm in the presence of a normal appearing co-twin. Color Doppler may show the presence of high-velocity, low impedance flow in the multicystic placental tissue. Maternal complications associated with CHM-CF include vaginal bleeding, hyperemesis gravidarum, thyrotoxicosis, early-onset severe preeclampsia, and thromboembolic disease[21,22].

Proposed Pathogenesis: The exact pathophysiologic process resulting in CHM-CF remains undetermined. While the majority of CHM-CF pregnancies are dizygotic, recent microsatellite marker studies demonstrated that 1 in 7 CHM-CF pregnancies are monozygotic[23]. In addition, cases of mosaicism resulting in CHM and normal fetuses have been described[24].

Gross Features: The placental tissue of CHM-CF pregnancies usually shows a sharp contrast between the grape-like clusters of cysts in the molar component and the age-appropriate normal appearance of the co-twin placenta (Figure 26.4a and b).

Microscopic Features: The molar component shows the typical characteristics of a complete hydatidiform mole: hydropic and avascular villi with hyperplastic, often circumferential and lace-like trophoblast, associated with large amounts of degenerating trophoblast (Figure 26.5a). The remainder of the placenta consists of unremarkable, age-appropriate villous tissue (Figure 26.5b). There is usually a clear demarcation between molar and normal villi, without evidence of intervening decidual tissue.

Ancillary Diagnostic Testing: If light microscopy is inconclusive, the presence of androgenetic diploidy in the molar component can be assessed by ancillary histopathologic techniques, such as immunohistochemical analysis of the paternally imprinted gene product p57/KIP2, or molecular genetic techniques (discussed in Chapter 4).

Prognostic Implications: The reported live birth rates among patients who do not terminate their pregnancies range between 16 percent and 56 percent[21,22]. Outcomes of higher order multiple CHM-CF pregnancies are generally worse than those of twin

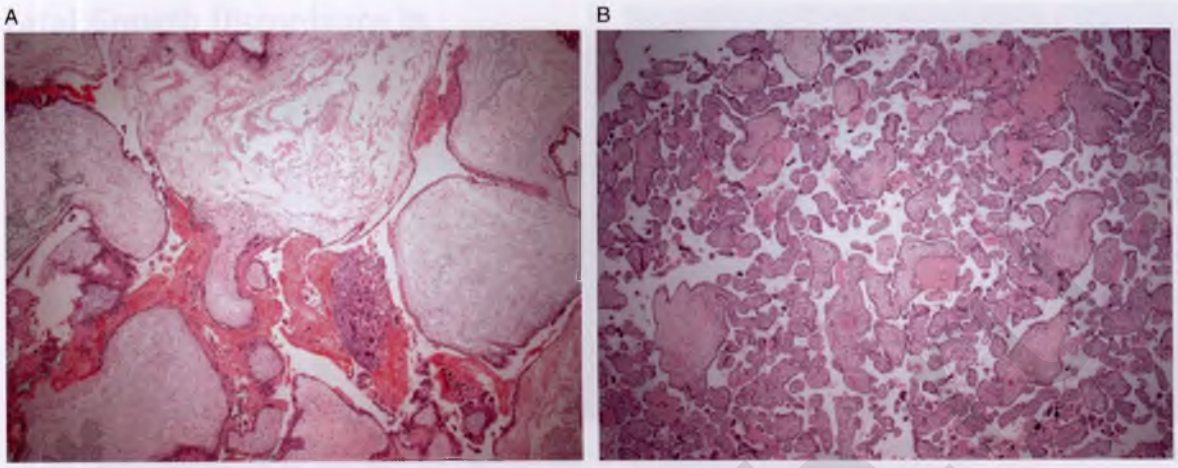

Figure 26.5 Histology of dichorionic pregnancy with complete hydatidiform mole. (a) Molar component showing markedly hydropic avascular villi with central cistern formation and prominent hyperplastic atypical trophoblast. (b) Normal placental parenchyma of the coexistent twin.

pregnancies[25]. Reported rates of persistent gestational trophoblastic disease in CHM-CF pregnancies range between 19 and 57 percent[22], compared with 14 to 16 percent for complete molar pregnancies alone. Termination of the pregnancy does not appear to lower the risk of persistent gestational trophoblastic disease.

Knowledge Gaps: Mechanisms underlying the development of a complete hydatidiform mole in association with a normal fetus, especially in the monozygotic context, remain unclear. Reliable imaging features and/or biomarkers predictive of fetal outcome and risk for persistent gestational trophoblastic disease remain to be determined.

Single Twin Demise: Vanishing Twin Syndrome and Fetus Papyraceus (Spontaneous Twin or Multiple Pregnancy Reduction)

Definition: Vanishing twin syndrome is the spontaneous loss of embryo or fetus during the first trimester of a twin or multiple pregnancy. Fetus papyraceus refers to the compressed, mummified fetal remnant of a twin or multiple pregnancy with death *in utero*, usually between 12 and 20 weeks' gestation.

Clinical Context: The diagnosis of vanishing twin syndrome is usually made when ultrasonographic identification of a twin pregnancy during the early first trimester is followed by observation of only one fetus at a subsequent ultrasound examination or at birth[26–28]. The true rate of vanishing twin syndrome in spontaneous multiple pregnancies is difficult to determine, but it may be as high as 29 percent[29]. The incidence of vanishing twin pregnancies after assisted reproductive technology (IVF-ICS) ranges between 10 and 30 percent[27,30]. Although usually asymptomatic, early fetal reduction may be accompanied by vaginal bleeding. Vanishing twin syndrome may have an impact on prenatal screening. Although studies reporting serum markers in pregnancies with a vanishing twin have been inconsistent, recent evidence suggests a 10–20 percent increase in plasma protein A, alpha-fetoprotein, and/or dimeric inhibin A levels[31]. Vanishing twin syndrome may also affect the interpretation of non-invasive prenatal testing based on cell-free fetal DNA. In this context, persistence of sex chromosome sequences of the vanishing twin may lead to misdiagnosis of fetal sex using cell-free fetal DNA analysis[32,33]. The incidence of fetus papyraceus is 1 in 200 twin pregnancies, compared with 1 in 12,000 pregnancies overall[34]. Fetus papyraceus occurs in both dichorionic and monochorionic twin or multiple pregnancies, with a trend toward higher frequency in association with monochorionicity and velamentous cord insertion[34,35]. Single-twin demise poses potential risks for the surviving co-twin, including increased risk of fetal demise, neurologic injury and risks associated with spontaneous and iatrogenic preterm birth, and with end-organ damage. The risk for the surviving twin is determined by two key influential factors: the gestational age at which

single fetal demise occurs, and the chorionicity of the multiple pregnancy[29].

Proposed Pathogenesis: The exact etiology of vanishing twin syndrome or of multiple pregnancy reduction later in gestation remains obscure in most cases. Fetal, maternal, placental, and iatrogenic factors may play a role[29]. Potential fetal causes of single intrauterine fetal demise (sIUFD) include discordant infections, discordant structural congenital anomalies (with or without chromosomal differences), and discordant fetal growth. The risk of sIUFD in growth-discordant pregnancies depends on estimated fetal growth discordance, fetal growth velocity and the presence of abnormal fetoplacental blood flow. Placental factors involved in sIUFD include uneven placental sharing, placental implantation anomalies, and peripheral cord insertion. Maternal factors include hypertensive disorders (e.g. preeclampsia), thrombophilia, and abruption. Iatrogenic sIUFD is seen after selective feticide and after laser therapy for TTTS.

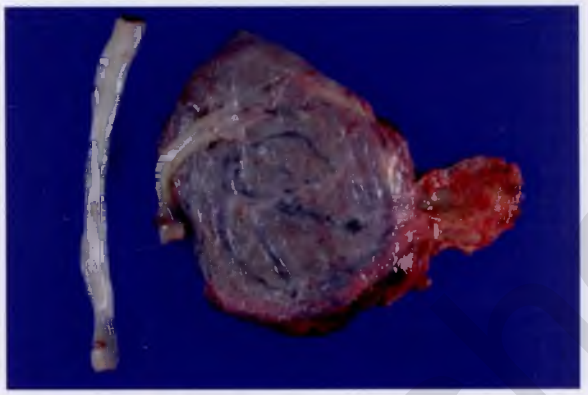

Figure 26.6 Diamniotic-dichorionic twin placenta of pregnancy complicated by "vanishing twin syndrome." A plaque-like density is present in the membranes, adherent to an apparently single disc.

Gross Features: The pathologic findings in single twin demise depend on the time of fetal death and the duration of *in utero* retention. Following early first trimester demise, a twin may vanish completely, without leaving any morphological residue. In such cases, genetic evidence of a resorbed twin may be detectable in the form of restricted placental chimerism[36]. In other cases, remnants of a second gestation may be present as a plaque-like thickening within the membranes or on the fetal surface of the placenta of the surviving co-twin (Figure 26.6). Ocular pigment may be the only clue to the existence of a macerated twin (Figure 26.7a and b). Remnants of a collapsed and partially resorbed gestational sac may be identified and occasionally contain embryonal or fetal tissue, such as degenerating vertebral column. The appearance of a fetus papyraceus greatly depends on the gestational age at demise and the duration of retention, as the deceased fetus may be progressively compressed by the growth of the co-twin (Figure 26.8a and b). While some are easily recognizable at delivery, others resemble amorphous necrotic material and may go unnoticed. Radiographs may be useful for documentation of skeletal remains. Profound maceration and post-mortem placental changes often preclude determination of cause of death.

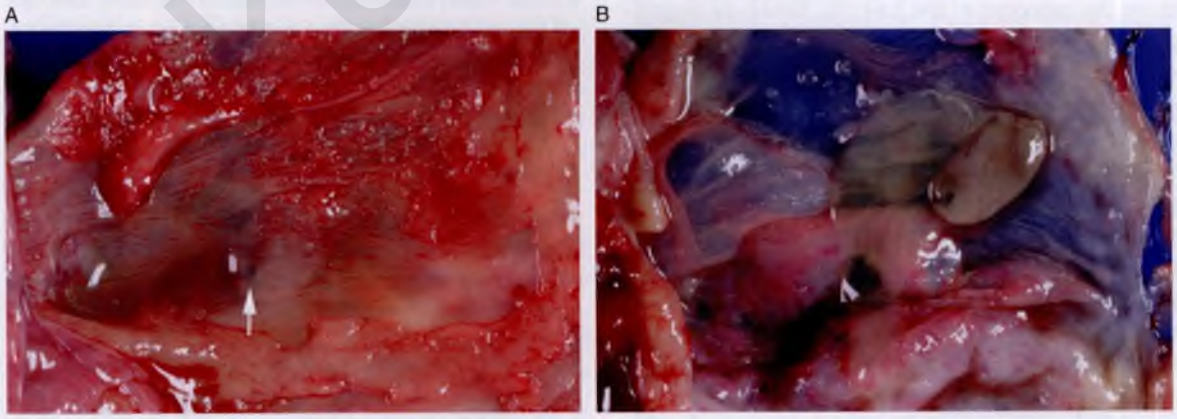

Figure 26.7 Diamniotic-dichorionic twin placenta of pregnancy complicated by "vanishing twin syndrome." (a) Closer view of plaque-like thickening shown in Figure 26.6, demonstrating the presence of ocular pigment (arrow). (b) Malformed embryo, representing the vanished twin.

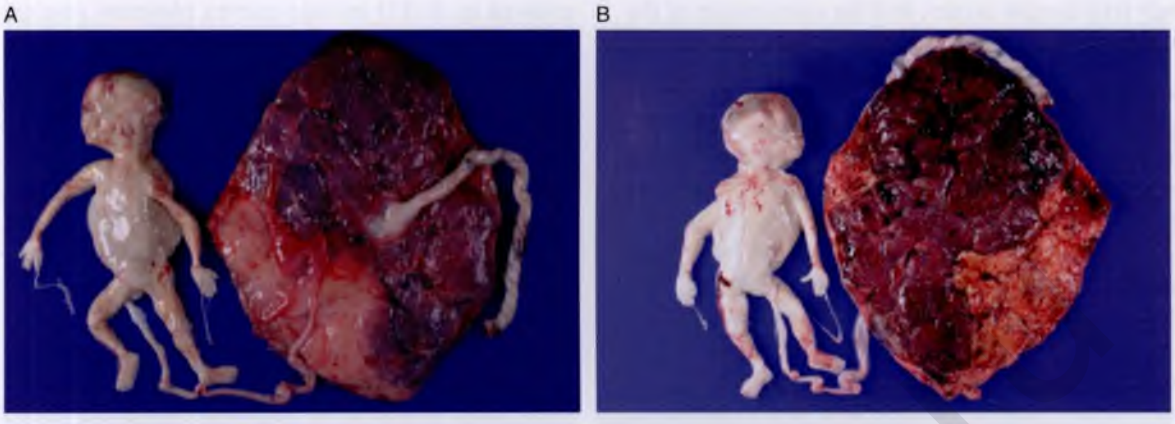

Figure 26.8 Diamniotic-dichorionic twin placenta with fetus papyraceus. (a) Partially mummified fetus and placenta (fetal side). (b) Maternal side of placenta showing changes related to intrauterine fetal demise.

Microscopic Features: Placentas from vanishing twin pregnancies may display nodules or well-delineated plaques of perivillous fibrin deposition, suggestive of remains of placental tissue of the resorbed twin(s). Fetal tissue remnants, degenerated placental villi or empty gestational sacs, located within the placental membranes or on the chorionic plate, may be seen in some cases. Microscopic examination of the inter-twin septum may establish chorionicity.

Ancillary Diagnostic Testing: Genetic testing of suspected remnants of a vanished twin may confirm pre-existing twin pregnancy and explain blood or other chimerism in the surviving - apparent singleton - twin.

Prognostic Implications: The timing of single twin demise and chorionicity are critical factors in determining the outcome of the co-twin. Evidence regarding the possible influence of a vanishing twin (early spontaneous reduction) on pregnancy and short- and long-term morbidity of the surviving co-twins is conflicting. Some studies found no differences in development between survivors of a vanishing twin pregnancy and singletons[35,37]. Other studies described adverse effects on growth and neurodevelopmental outcome in the surviving twins, with higher risk when the fetal loss occurred at later gestational ages (> 8 or 12 weeks),[30,38] and in monochorionic pregnancies[39]. The perinatal outcome may be worse for vanishing twin pregnancies after IVF-ICSI (intracytoplasmic sperm injection) compared with spontaneously conceived pregnancies[40]. The outcome of twin pregnancies following second or third trimester single fetal demise is mainly determined by chorionicity. Overall, the odds of co-twin intrauterine death following twin demise are 6 times higher in monochorionic twins than in dichorionic twins, and monochorionic twins are more than four times more likely to have neurodevelopmental morbidity[41,42]. The reported rates of preterm delivery are 68 and 54–57 percent, respectively, for monochorionic and dichorionic surviving twins[41,42].

Knowledge Gaps: The correlation between placental angioarchitecture and fetal morbidity and mortality of the surviving co-twin after sIUFD in monochorionic twin pregnancies are unclear. Optimal management approaches, in particular ideal timing of delivery of surviving twin following sIUFD in monochorionic twin pregnancies, remains to be determined. Determination of the effects of early and late sIUFD on long-term (neuro)developmental outcome awaits large, controlled cohort studies.

Triplets / Higher Order Multiple Gestations

Definition: Pregnancy composed of ≥ 3 fetuses. The placentas may have separate or shared discs, separate or shared chorions, and separate or shared amniotic sacs.

Clinical Context: Between 1980 and 1997, twin births in the United States rose by more than 50 percent, and triplet births by over 400 percent[43]. This dramatic increase was ascribed to older maternal age distribution and therefore increased use and availability of

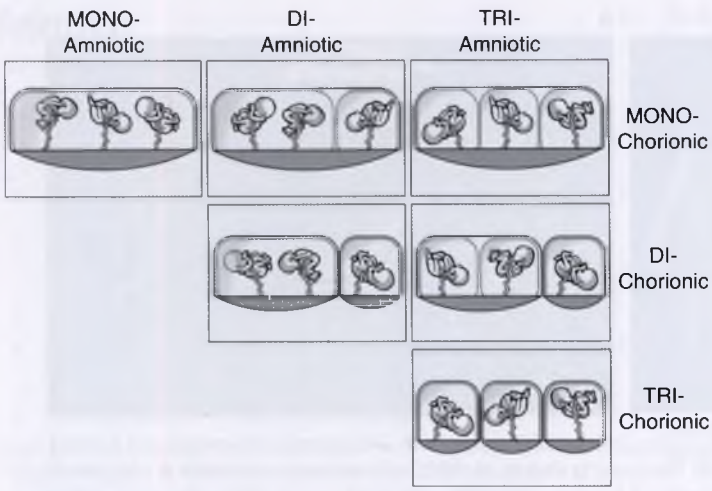

Figure 26.9 Patterns of triplet pregnancy (artwork by Francois Luks, MD, PhD).

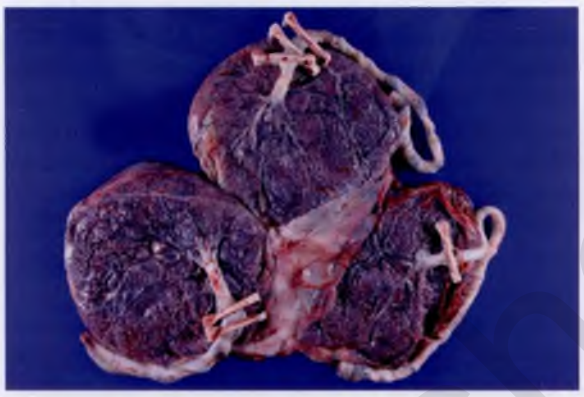

Figure 26.10 Triamniotic-trichorionic triplet placenta. Triplet placenta composed of three fused placentas with separate amnions, chorions and vasculature.

fertility therapies, including assisted reproductive technologies (ART) (e.g. in vitro fertilization [IVF]) and non-ART treatments (e.g. ovulation stimulation). More recently, triplet and higher order multiple birth rates have declined because of multifetal pregnancy reduction and modified ART procedures with transfer of a reduced number of embryos per IVF cycle[43,44]. According to recent data, multiple births now comprise 3–4.5 percent of all births[44]. The policy of restricting the number of transferred embryos has led to a reduction in the rate of trichorionic triplets, but may have increased the relative proportion of triplets with mixed chorionicity because of the higher proportion of triplets resulting from the splitting of one of the two embryos or blastocysts replaced[45]. A multifetal pregnancy can undergo spontaneous reduction ("vanishing twins"), usually in the first 11–12 weeks of pregnancy. Selective iatrogenic reduction of multifetal pregnancies is usually performed in the first trimester of pregnancy (after 12 weeks). Methods for fetal reduction include intrathoracic or intracardiac potassium chloride injection and laser or radiofrequency ablation of pelvic vessels. Multifetal pregnancy reduction (from three to two fetuses) in trichorionic triplets results in a lower risk of severe preterm delivery, but is associated with a higher miscarriage risk[46].

Proposed Pathogenesis: Higher order multiple births may be spontaneous (linked to polyovulation) or iatrogenic (associated with assisted reproductive technology and ovulation induction).

Gross Features: Triplets and higher order multiples and their placentas may have any combination of zygosity and chorionicity. Proposed terminology to describe triplet placentation includes the number of amnions and number of chorions, followed by a description of the twins in a monochorionic relationship, if applicable (e.g. quadramniotic-trichorionic quadruplet placenta, diamniotic-monochorionic for quadruplets A and B). Triplet placentas may be monochorionic, dichorionic, or trichorionic, with all possible combinations of amniotic sacs (Figure 26.9–26.11). The majority of triplet pregnancies are trichorionic, where each fetus has its own placenta and amniotic cavity (Figure 26.10). Monozygous triplets may be monoamniotic, diamniotic, or triamniotic. Dizygous triplets may be dichorionic or trichorionic. Trizygous triplets are virtually always trichorionic. Combinations

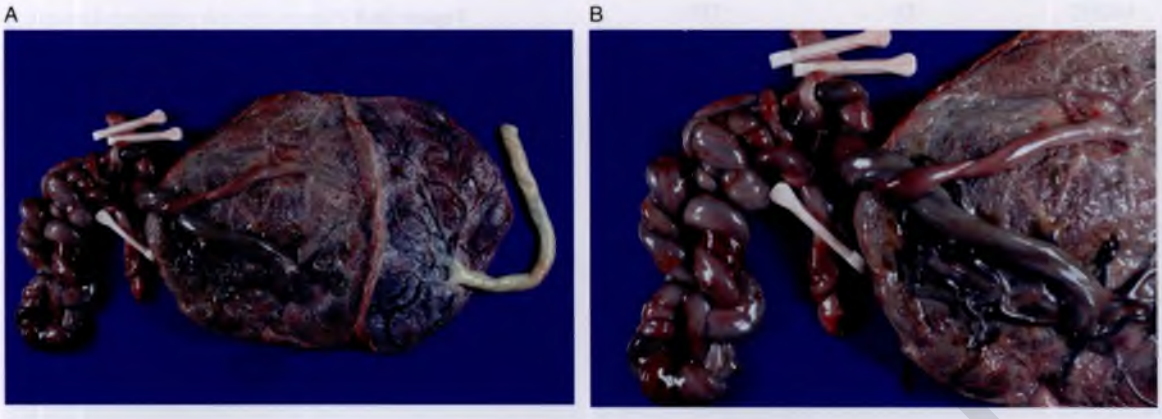

Figure 26.11 Two stillborn triplets in a monoamniotic-monochorionic relationship (left, with entangled cords) are separated from the third (viable) triplet by a firm ridge and thick dividing membrane. The surviving sib is multi-chorionotic/amniotic with respect to non-surviving co-sibs.

of monozygous and polyzygous multiples are common. Space constraints associated with higher order multiple pregnancies result in unfavorable placental implantation, and increased frequency of intertwin placental growth discordance, extreme peripheral (marginal or velamentous) cord insertion, and placental fusion. Reduced fetuses may be identified after spontaneous or selective multifetal pregnancy reduction. Reference values for weights of triplet placentas have been established[47].

Microscopic Features: The histopathologic findings in higher order multiple placentas are variable, and mainly influenced by associated placental anatomic characteristics, such as cord insertion type and placental size. The findings may be confounded further by chronic or acute twin-to-twin transfusion between monochorionic twins. Microscopic examination of any inter-twin membranes aids in establishment of placentation type.

Ancillary Diagnostic Testing: Zygosity studies are indicated, as in all multiple gestations. Placental vascular injection studies for monochorionic multiplets are optional.

Prognostic Implications: The perinatal mortality risk of higher order multiples is 10- to 12-fold higher than that of singletons[43,48]. The primary explanation for the high mortality risk is the increased rate of prematurity in multiples, with increased intrauterine growth restriction as a secondary influence[43,49,50]. Multiples are also at higher risk for long-term complications, including cerebral palsy, cognitive impairment, neurodevelopmental delay, and social behavior difficulties[51,52]. The risk for cerebral palsy correlates with the number of fetuses, with plurality having an exponential effect on risk. The risk of morbidity and mortality in multiple pregnancies is further increased by monochorionicity[53]. Triplets with mixed chorionicity are at a higher risk of intrauterine fetal death, fetal growth restriction, weight discordance, and preterm delivery than trichorionic triplets[54]. In monochorionic multiples, placental sharing and the presence of inter-twin vascular communications may result in TTTS, twin anemia-polycythemia sequence, or selective intrauterine growth restriction. As in monochorionic twin gestations, these conditions primarily contribute to the excess morbidity in multiple pregnancies that include a monochorionic pair[55]. Multiple pregnancies are associated with poorer maternal outcomes and increased obstetrical complications, including preterm labor and delivery, gestational hypertension and preeclampsia, gestational diabetes, placental abruption, and excessive postpartum bleeding[56].

Knowledge Gaps: The mechanisms of congenital anomalies in multiple pregnancies remain unclear. There is a lack of data regarding the effect of fetal reduction and the different reduction approaches on long-term survival and neurodevelopmental outcome among multiplet gestations. The relative contribution of multiplicity versus factors related to underlying infertility and/or factors related to reproductive technology to the observed adverse pregnancy outcome of multiple pregnancies remains unclear.

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Chapter 27

Abnormal Placental Location

Kelly Devereaux and Ann Folkins

Abnormal Placental Location (Placenta Previa, Tubal Ectopic Pregnancy, Nontubal Ectopic Pregnancy)

Definition: Abnormal placental location is defined as suboptimal implantation site associated with maternal, fetal, and neonatal morbidity and mortality. Abnormal implantation occurs at both intrauterine (placenta previa) and extrauterine locations (ectopic pregnancies) (Table 27.1).

Placenta Previa

Definition: Implantation in the lower uterine segment, resulting in a placenta overlying (partial or total placenta previa) or within 2 cm of (marginal placenta previa) the internal cervical os. In some cases, it is only a succenturiate, accessory placental lobe that is located at this site. The term placenta previa is named for the succession in which the placenta is delivered "previous" to the neonate.

Clinical Context: Placental previa is estimated to occur in 0.5 percent of pregnancies[1,2]. There are several well-established predisposing risk factors, most notably prior cesarean section (Table 27.2). Women typically present asymptomatically or with second or third trimester painless vaginal bleeding, and diagnosis is made by transvaginal ultrasound. Some cases of placenta previa resolve with lower uterine segment development and "apparent" placental migration. Such resolution is less likely when the placenta is posterior or in the setting of a prior cesarean section. Management typically requires delivery by cesarean section (hopefully before labor) between 36 and 39 weeks depending on overall maternal and fetal health[3]. Placental complications known to be associated with placenta previa include placenta accreta and vasa previa.

Proposed pathogenesis: The pathophysiology of placenta previa remains largely speculative. It has been hypothesized that alterations in the intrauterine environment lead to implantation in the lower uterine segment and internal cervical os. Specifically, endometrial damage or scarring may be contributory[2]. In addition, suboptimal placental perfusion may also play a role in this phenomenon[4].

Gross features: The placenta will either be completely or partially implanted over the internal cervical os and may show a retroplacental hematoma in this area due to prior bleeding (Figure 27.1). Other complications known to be associated with placenta previa should be

Table 27.1 Types of abnormal placental location

Intrauterine site (0.5% of pregnancies)	Extrauterine sites (ectopic) (1–2% of pregnancies)
Placenta previa	Tubal (95% of ectopic pregnancies)
	Non-tubal (5% of ectopic pregnancies)
	Cervical
	Ovarian
	Abdominal
	Cornual
	Cesarean scar (discussed in Chapter 28)

Table 27.2 Risk factors for placenta previa

- Multiparity
- Prior cesarean delivery
- Advanced maternal age
- Multiple gestations
- Infertility treatment
- Previous placenta previa
- Spontaneous and elective pregnancy termination
- Prior uterine surgery or damage (e.g. myomectomy)
- Smoking
- Cocaine

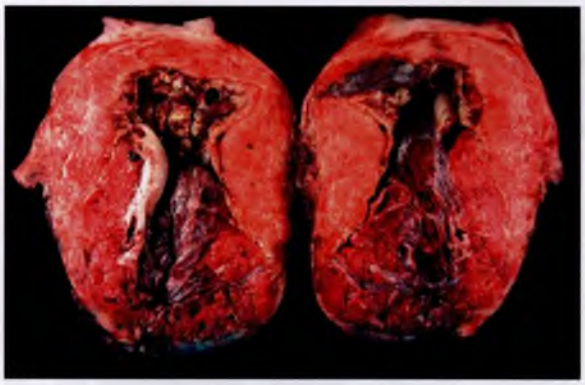

Figure 27.1 Bivalved uterus with *in situ* placenta previa. The cervical os is at the bottom of the picture.

assessed for grossly, including placenta accreta, vasa previa, circumvallation, and abnormal cord insertion. In addition, features of fetal growth restriction (e.g. low placenta weight) may be present.

Microscopic Features: The diagnosis of placental previa is primarily based on the gross relationship of the placenta to the cervical os. In a hysterectomy specimen, a microscopic section of the placenta adjacent to the cervix is useful for documentation. Plasma cell deciduitis can often be seen in these cases.

Ancillary Diagnostic Testing: None are currently used.

Prognostic Implications: Placenta previa is associated with both maternal and fetal complications predominately secondary to maternal hemorrhage. Complications resulting from maternal bleeding include a need for blood transfusion, hysterectomy, maternal intensive care unit admission, septicemia, thrombophlebitis, fetal underperfusion, and maternal death. Many of the fetal complications are associated with prematurity, given that 40 percent of woman typically require delivery prior to 38 weeks[3]. In fact, placenta previa has been associated with an increase (fivefold) in prematurity rates, NICU admissions, and peri/neonatal death compared to patients without placenta previa[5]. There is apparently no increase in neonatal morbidity or mortality associated with placenta previa once there is correction for gestational age[6].

Knowledge Gaps: The cause of placenta previa remains largely unknown. A better understanding of implantation and placental physiology may help explain why placenta implantations occur at this site. Additionally, in some instances of placenta previa, the low-lying placentas will resolve; however, this is challenging to predict and requires further investigation.

Ectopic Pregnancy

Definition: Extrauterine or ectopic pregnancy is defined as implantation and gestational development outside of the endometrial cavity. Sites of implantation include the fallopian tube, cervix, ovary, abdomen, cornu (rudimentary horn), and cesarean scar (Table 27.2). Extremely rare cases of retroperitoneal implantation have also been reported. Cesarean scar ectopics are discussed in Chapter 28; the other sites are covered in the following sections.

Clinical Context: Ectopic pregnancies account for approximately 1–2 percent of all pregnancies and are clinically suspected when serum beta-human chorionic gonadotropin (β-hCG) levels are elevated in the absence of an intrauterine pregnancy by ultrasound[8]. Occasionally, additional imaging by MRI or exploratory laparotomy is required to make a definitive diagnosis. Early diagnosis and management is essential to prevent serious life-threatening risks, such as rupture, severe hemorrhage, and shock. Generally, termination in the first trimester is recommended, given their high-risk nature. Depending on location, gestational age, and maternal health, ectopic pregnancies are managed expectantly (e.g. when stable and β-hCG is low or declining), pharmacologically (e.g. methotrexate), or surgically (e.g. laparoscopy).

Ectopic pregnancies are believed to be multifactorial in origin with several well-known risk factors (Table 27.3). However, the majority of women will have no identifiable risk factors, suggesting that there are additional contributory factors that are not yet known[9]. Unique clinical features at each ectopic pregnancy site are detailed below.

Tubal Ectopic Pregnancy: Tubal pregnancies are the most common type of ectopic pregnancy and the leading cause of maternal morbidity and mortality during the first trimester of pregnancy[9,10]. Implantation occurs most frequently in the ampulla (70 percent), followed by the isthmus (11 percent), fimbrial (12 percent), and interstitial (3 percent) portions of the tube.[11] At diagnosis, patients may be entirely asymptomatic (intact tubal pregnancy) or may present with nonspecific symptoms such as pelvic

pain, vaginal bleeding, nausea, and/or hemorrhagic shock (ruptured ectopic pregnancy)[9,10].

Cervical Pregnancy: Cervical pregnancies are extremely high risk and are associated with life-threatening hemorrhage secondary to rupture or erosion of the cervical branches of the uterine arteries[12, 13]. Patients typically present with vaginal bleeding and abdominal pain, and on examination show a distended or engorged cervix with an open os, which can be easily misdiagnosed as a miscarriage[13]. More advanced-stage cervical pregnancies may require a hysterectomy[13,14]. The number of cases has increased over time with a rise in the rate of dilation and curettage and in vitro fertilization[13]. Additional risk factors specific to cervical pregnancies include Asherman's syndrome and uterine anatomic abnormalities (leiomyomata, synechiae)[12].

Table 27.3 Ectopic pregnancy implantation sites

Type	Location
Tubal	Interstitial (intramural), ampullary, isthmus or fimbriated portions of the fallopian tube
Cervical	Endocervical mucosa below the level of the internal cervical os
Ovarian	Intra- or extrafollicular ovarian tissue
Abdominal	Pouches surrounding the uterus (e.g. pouch of Douglas), serosa of the uterus and adnexa, omentum, bowel and appendix, liver, spleen, and abdominal wall (listed from most to least common sites[7])
Cornual	By anatomic definition, refers to implantation in the cornu of the uterus, whether the anatomy is normal or contains a congenital Mullerian duct abnormality
Cesarean scar	Implantation at the site of a previous cesarean section scar

Ovarian Pregnancy: Although most ovarian pregnancies are detected in the first trimester, nonruptured second and third trimester pregnancies have been reported, possibly owing to the thick, tensile nature of the ovarian capsule[15]. Patients typically present with nonspecific symptoms such as abdominal pain, and the diagnosis is challenging, as ultrasound findings will often mimic those of a corpus luteum cyst, hemorrhagic cyst, endometriotic cyst, or various other ovarian pathologies. Even when an ectopic pregnancy is suspected, an ovarian pregnancy can often be difficult to distinguish from a tubal pregnancy that is tightly adjacent to the ovary[16,17]. A definitive diagnosis is typically made surgically and histologically.

Abdominal Pregnancy: Abdominal pregnancies present with nonspecific findings, and half of the cases cannot be diagnosed by ultrasound[18]. In fact, many require MRI or exploratory laparoscopic surgery for definitive diagnosis[18]. Advanced second and third trimester abdominal pregnancies are rare; however, there have been several case reports of live births. When the diagnosis is made after 20 weeks, expectant management may be considered with delivery at 34 weeks if patient is healthy and can undergo close medical observation.[19] During surgical delivery, a firmly implanted placenta is often left in place, given the high risk of hemorrhage. Any retained placenta is at risk of infection and is typically managed with embolization and/or administration of methotrexate[19–21].

Cornual (Rudimentary Horn) Pregnancy: The terms "interstitial pregnancy" and "cornual pregnancy" are often used inconsistently and synonymously in the literature, although they are anatomically distinct locations. "Interstitial" describes the intramural segment of the fallopian tube, whereas

Table 27.4 Ectopic pregnancy risk factors

Surgical	Medical	Toxins	Infections	Other
Pelvic/abdominal surgery	Endometriosis	Smoking	Pelvic inflammatory disease	Age
Tubal surgery	Infertility	Cocaine	Neisseria gonorrhea	Assisted conception/ in vitro fertilization
Termination of pregnancy			Chlamydia trachomatis	Intrauterine device
Sterilization				

"cornual" refers to the superior-lateral area of the uterine cavity adjacent to the fallopian tube entrance[22]. The term "cornual" is also applied to pregnancies in a bicornuate or septate uterus as well as the rudimentary horn of a unicornuate uterus, which may or may communicate with the uterine cavity. By any aforementioned definition, these pregnancies can be challenging to diagnosis, as they are often misdiagnosed as intrauterine pregnancies and present at more advanced stages when there is significant risk of rupture. Often cornual pregnancies are diagnosed at later gestational ages when methotrexate is not indicated. Therefore, primary treatment options include myomectomy, cornuotomy, cornual resection, or excision of the rudimentary horn[13].

Proposed Pathogenesis: The etiology of ectopic pregnancy is largely unknown, but likely involves alterations in the normal implantation physiology, possibly secondary to toxins, infectious microorganisms, hormones, or increased inflammation.

Tubal Ectopic Pregnancy: Tubal implantation is often due to physical obstruction or impaired motility (dysfunctional smooth muscle contraction and/or ciliary beating) which leads to impaired embryotubal transport. In addition, alterations in signaling may lead to aberrant ovum chemotaxis and implantation[10,19,23].

Cervical *Ectopic Pregnancy*: Implantation in the endocervical canal mucosa is likely caused by physiologic changes or pathology in the endometrial cavity or cervix.

Ovarian *Ectopic Pregnancy*: Primary ovarian pregnancy is hypothesized to occur during ovulatory dysfunction and/or interference of the ovum release from the ruptured follicle and subsequent fertilization within the follicle. Specifically, thickening of the tunica albuginea by local inflammation may promote such trapping[24–26]. Alternatively, these pregnancies may occur secondary to dysfunctional fallopian tubal motility and retrograde transport of the fertilized ovum to the ovary[24,25]. Ovarian pregnancies may be intrafollicular and extrafollicular. Extrafollicular pregnancies are more common and believed to be secondary or primary in origin, while the intrafollicular type is likely exclusively primary[13, 25].

Abdominal *Pregnancy*: Abdominal pregnancies may be primary or secondary. In primary abdominal pregnancy, fertilization and implantation both occur in the abdomen. It has also been postulated that alteration in the flow of the peritoneal fluid can misdirect the ovum to the posterior cul-de-sac (pouch of Douglas), leading to intra-abdominal fertilization and implantation[27]. In the secondary form, the fertilized ovum is extruded into the abdominal cavity with subsequent implantation. This may occur by failed retention or retrograde movement of the ovum within the fallopian tube[28]. Ovum displacement via a uterine fistula tract or dissemination through lymphatic channels are other proposed mechanisms[29–31].

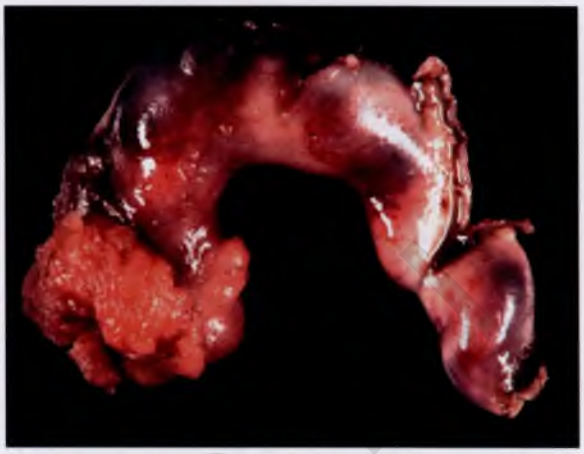

Figure 27.2 Intact ectopic tubal pregnancy with distended fallopian tube and dusky serosal surface.

Cornual (*Rudimentary Horn*): Impairment in normal implantation physiology may lead to implantation in the cornu. In a noncommunicating rudimentary horn, implantation is believed to occur via transperitoneal migration of the fertilized oocyte.

Gross Features: The gross findings of nontubal ectopic pregnancies depend on the site and gestational age.

Tubal *Pregnancy*: A partial or complete salpingectomy is typically performed. The affected segment of the fallopian tube may appear distended or cystic at the site of the gestational sac pregnancy with congested or dusky overlying serosa (Figure 27.2). The intraluminal contents contain blood (hematosalpinx) with associated villous material. The wall of the fallopian tube may be thinned or ruptured, and the condition of the tube (intact versus ruptured) should be documented (Figure 27.3).

Cervical Pregnancy: Cervical pregnancies are usually amendable to curettage at early gestational stages, and thus the gross findings are of typical products of conception. If a hysterectomy is performed, the placental tissue should be attached to the cervix

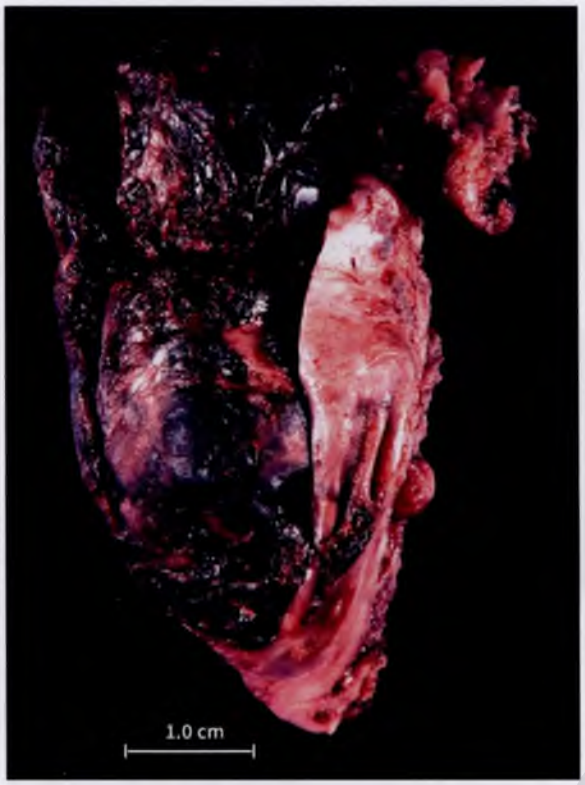

Figure 27.3 Ruptured ectopic tubal pregnancy with organizing hemorrhage on the left side of the image and fallopian tube fimbriae in the upper right aspect.

below the uterine vessels and the peritoneal reflections[32].

Ovarian *Pregnancy*: Surgical treatment of an ovarian pregnancy typically requires a partial or total oophorectomy with or without a salpingectomy. The ovarian tissue may appear congested and hemorrhagic and contain a cyst-like structure on the outer surface with inner contents consistent with products of conception. The condition of the ovary (ruptured versus intact) should be documented.

Abdominal Pregnancy: The gross appearance of an abdominal pregnancy will depend on the duration of the gestation and location of the implantation and whether those involved organs are resected as well.

Cornual Pregnancy: Cornual pregnancies are sometimes resected with a portion of the myometrial wall and are usually fragmented.

Microscopic Features: In general, ectopic pregnancies demonstrate chorionic villi and implantation site in conjunction with adjacent maternal tissues appropriate for the ectopic site. Variable fetal parts may be identified depending on the gestation age. Often the products are viable, not necrotic, as compared with missed and spontaneous abortions.

Tubal Pregnancy: In situ tubal ectopic pregnancies are hemorrhagic (often with hematosalpinx), with intraluminal chorionic villi, extravillous trophoblasts (may be degenerated), tubal implantation site, and variable fetal parts (Figure 27.4). Evidence of rupture should be documented.

Cervical Pregnancy: Cervical pregnancies can be confirmed by the presence of cervical glands adjacent to the placental implantation site (Figure 27.5).

Ovarian Pregnancy: The diagnosis of an ovarian pregnancy relies on histologic confirmation of chorionic villi and trophoblastic tissue within the ovarian stroma (Figure 27.6)[33]. Evidence of rupture should be documented.

Abdominal Pregnancy: Findings will depend on gestational age and site of implantation.

Cornual Pregnancy: If surgically resected, microscopic finding may contain products of conception with implantation site changes within the adjacent myometrium.

Ancillary Diagnostic Testing: None are currently used. However, several biomarkers (e.g. proteins, mRNA and microRNAs) are under investigation with the hope of identifying a unique signature that can distinguish pregnancies at ectopic sites from normal intrauterine pregnancies and miscarriages[19,34].

Prognostic Implications: Ectopic pregnancies account for 9 percent of pregnancy related deaths in the United States[35]. When not detected and managed early, ectopic pregnancies are at risk of rupture, which can lead to life-threatening consequences such as hemorrhage, shock, and disseminated intravascular coagulation (DIC). When surgically managed, incomplete removal of the ectopic pregnancy and retention of trophoblastic tissue can lead to persistent ectopic pregnancy (PEP) and requires additional surgical or pharmacologic treatment with methotrexate to prevent potentially fatal hemorrhage[36–39].

Knowledge Gaps: Due to the rarity of nontubal ectopic pregnancies, the etiology of aberrant implantation and embryonic development is largely speculative. A better understanding of normal implantation physiology and how certain known risk factors (e.g. smoking, infection, or exogenous

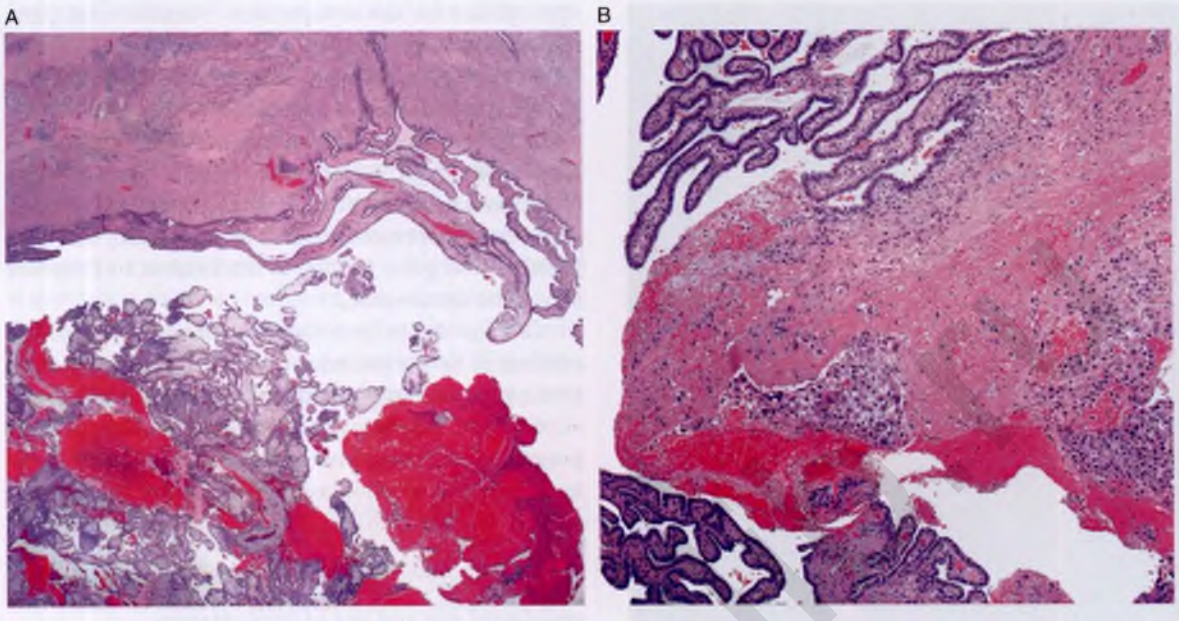

Figure 27.4 Ectopic tubal pregnancy. (a) Low-power image of chorionic villi within the fallopian tube lumen in ectopic pregnancy. (b) Implantation site in the fallopian tube plicae.

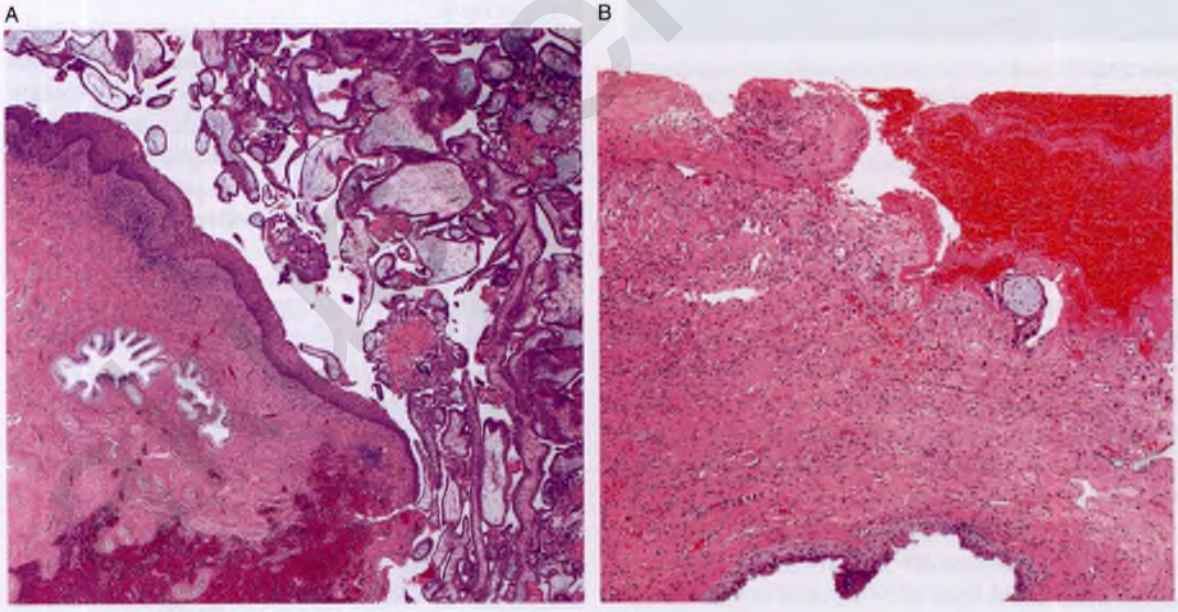

Figure 27.5 Ectopic cervical pregnancy. (a) Low-power image of chorionic villi adjacent to the cervical os. (b) Implantation site with a chorionic villus at the top of the image adjacent to an endocervical gland with tubal metaplasia at the bottom of the image.

infertility hormones) alter this process is critical to developing preventative measures. Additionally, novel molecular biomarkers are needed to help diagnose ectopic implantations as well as predict the success of methotrexate or expectant management in ectopic pregnancy treatment.

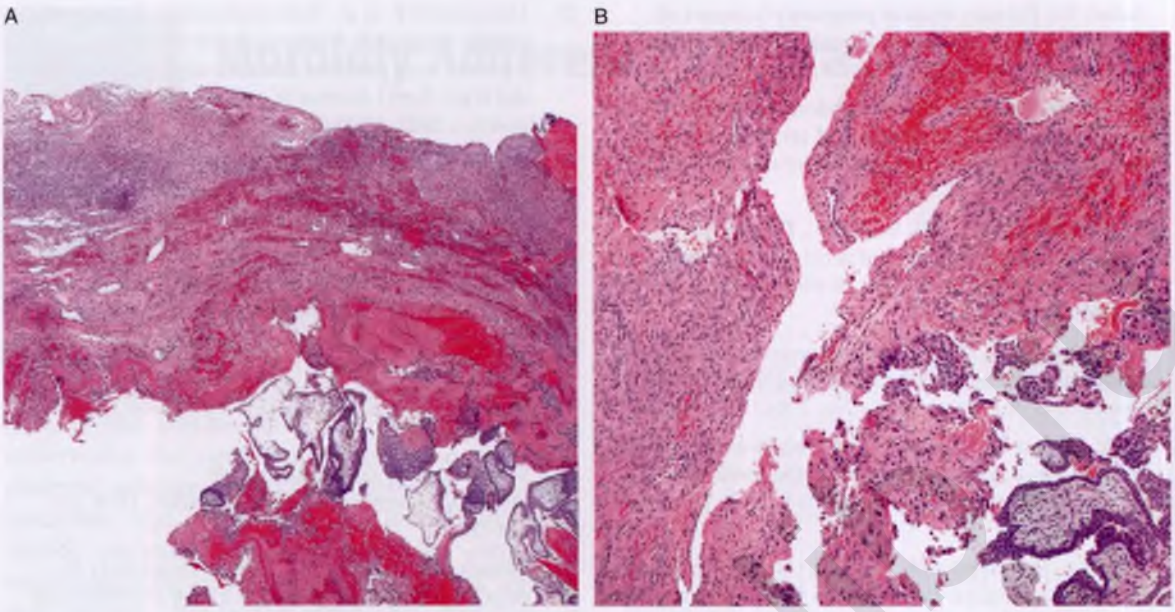

Figure 27.6 Ectopic ovarian pregnancy. (a) Low-power image of chorionic villi and implantation site at the bottom of the image with adjacent ovarian stroma in the upper part of the image. (b) Closer view of chorionic villi and implantation site in the ovarian stroma.

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Chapter

28 Morbidly Adherent Placenta

Linda M. Ernst

Morbidly adherent placenta (MAP) is the newest clinical terminology referring to the spectrum of diseases associated with abnormal placental adherence to the uterine wall. This new terminology underscores the significant contribution abnormal placental adherence makes to maternal and fetal morbidity and mortality. The lesions of MAP include placenta creta, an overarching term that encompasses the entities of placenta accreta, increta, and percreta. While the pathologic diagnoses of placenta accreta, increta, and percreta are typically made on hysterectomy specimens, there is increasing evidence in the literature that lesions in the spectrum of MAP can be diagnosed via examination of the delivered placenta. The careful examination of the basal plate of the delivered placenta can identify areas of adherent myometrial fibers[1-5] with or without an adequate intervening decidual layer. Table 28.1 shows a staging system for MAP that includes abnormal placental adherence identifiable in the delivered placenta in addition to diagnoses made on hysterectomy. This chapter will focus on lesions within the spectrum of MAP and related entities, cesarean scar pregnancy and retained placenta.

Table 28.1 Pathologic staging of MAP

Stage	Definition
1	Basal plate with adherent myometrial fibers Placental basal plate with adherent myometrial fibers and intervening decidua present
2	Changes suggestive of placenta accrete ≤ 2 layers of decidual cells separating myometrium from anchoring villi and/or Rohr's fibrinoid, but not diagnostic for accrete
3	Changes consistent with histologic placenta accrete Anchoring villi and/or Rohr's fibrinoid in contact with myometrial fibers
4	Placenta increta with invasion into the myometrium A = <25% B = 25 – 50% C = 50 – 75% D = 75 – 100%
5	Placenta percreta but no involvement of adjacent organs
6	Invasion/attachment of adjacent organs identified

Placenta Accreta, Increta, Percreta (Morbidly Adherent Placenta, Placental Attachment Disorders[6], Placenta Creta)

Definition: Placenta accreta is characterized by the abnormal implantation of chorionic villi upon the superficial myometrium without an intervening decidual layer. *Total placenta accreta* is defined by involvement of all placental lobules. *Partial placenta accreta* involves at least 2, but not all placental lobules, and *focal placenta accreta* involves only one lobule, either partially or entirely[7]. Placenta increta is diagnosed when chorionic villi "invade" or extend into the myometrium, and placenta percreta is defined by full thickness penetration of the myometrium and serosa with or without attachment and penetration of adjacent organs. Accreta represents about 75 percent of MAP, increta 18 percent, and percreta 7 percent[8].

Clinical Context: The reported incidence of MAP varies up to as frequently as 3/1000 pregnancies[8]. A recent large multicenter cohort study reported an incidence of 1/731 births[9]. The increasing rate of cesarean section is generally believed to contribute

to the increasing incidence of MAP. Furthermore, the incidence of accreta increases with each additional cesarean section delivery, ranging from 0.24 percent incidence with the first cesarean section and up to 6.74 percent in women who have had 6 or more cesarean sections[10]. Moreover, the risk of accreta when placenta previa is present is 3 percent, 11 percent, 40 percent, 61 percent and 67 percent for the first, second, third, fourth, and fifth or more repeat cesarean sections, respectively[10]. While cesarean section and placenta previa pose the greatest risk for MAP, other forms of endometrial/myometrial injury also contribute to MAP. Therefore, uterine instrumentation such as myomectomy, dilation and curettage (D&C), or endometrial ablation as well as conditions such as Asherman syndrome and submucosal leiomyoma are risk factors for MAP[7]. Advanced maternal age has also been reported to be an independent risk factor for accreta[11]. Prenatal diagnosis of MAP is primarily made on sonogram. Concerning features in the first trimester include gestational sac in the lower uterine segment and irregular vascular spaces in the placental bed. Later in gestation, loss of the normal hypoechoic retroplacental zone, increased subplacental vascularity, abnormalities of the interface between the uterus and the bladder, retroplacental myometrial thickness <1 mm, and multiple vascular lacunae in the placenta are some of the sonographic features that suggest MAP[12,13]. MRI can also be used in prenatal diagnosis of MAP, but whether it improves diagnostic accuracy is unclear[14,15]. In a recent large cohort study, MAP was suspected prenatally in only 53.2 percent of women who were ultimately diagnosed with MAP; however, when MAP was suspected prenatally there was significantly more morbidity[9]. These results suggest prenatal imaging studies are best at detecting the severe forms of MAP. The morbidly adherent placenta is difficult, and sometimes impossible, to separate from the uterus at delivery which can lead to significant hemorrhage. In addition, surgical complications and severe placenta invasion as seen in placenta percreta can lead to injury of adjacent organs. Accordingly, complications of MAP include massive obstetrical hemorrhage, need for multiple transfusions, shock, disseminated intravascular coagulation, intensive care unit admission, cystotomy, bowel injury, ureteral injury, and ileus[8,10]. When the placenta cannot be separated from the uterus or bleeding cannot be controlled, hysterectomy is required. Currently, the most common indication for cesarean hysterectomy in many centers is placenta accreta[16–18]. Management of patients with a MAP is best handled at major medical centers (centers of excellence) with a multidisciplinary team, large blood bank services, and experienced intensive care unit staff[9,12,19]. Hysterectomy is required in up to 70 percent of women with MAP[9]. Other more conservative options include leaving the placenta in situ/expectant management, uterine artery ligation, hypogastric artery ligation, balloon tamponade, B-Lynch suture, uterotonics, and hysteroscopic resection of retained placenta[9,20] Preparations for conversion to immediate hysterectomy are recommended with all conservative approaches[20].

Proposed Pathogenesis: The exact pathogenic mechanisms involved in MAP have not been fully delineated; however, based on the clinical risk factors described above, the most accepted theory proposes that defective decidualization of the endometrium is a key factor in the formation of accreta. Proper decidualization entails morphologic and biochemical reprogramming of endometrial stromal cells which leads to their ability to regulate trophoblast invasiveness, resist inflammatory insults and oxidative stress, and dampen the maternal immune response[21]. As such, implantation site decidua plays an important role in both implantation and placental separation. The normal placental implantation site contains the decidual layer known as the separation zone, located adjacent to Nitabuch's fibrinoid. This layer separates from the uterus secondary to the shearing action of the uterine contractions during normal labor and delivery[16] (Figure 28.1). Anatomically, the uterine fundus is the ideal site for implantation of the placenta with ideal vascularization and decidualization of the endometrium. The lower uterine segment of the uterus is not the ideal environment for implantation, and is believed to have less well-developed decidua. Furthermore, injury to the endometrium and myometrium from trauma or surgical procedures such as cesarean section, curettage, and myomectomy may lead to scar and the inability to regenerate adequate endometrium which can adversely affect decidualization[22]. Abnormal immune regulatory mechanisms have also been postulated to be associated with MAP. Reduced numbers of decidual natural killer cells and increased numbers of regulatory T-cells have been reported in MAP[23,24]. These immune

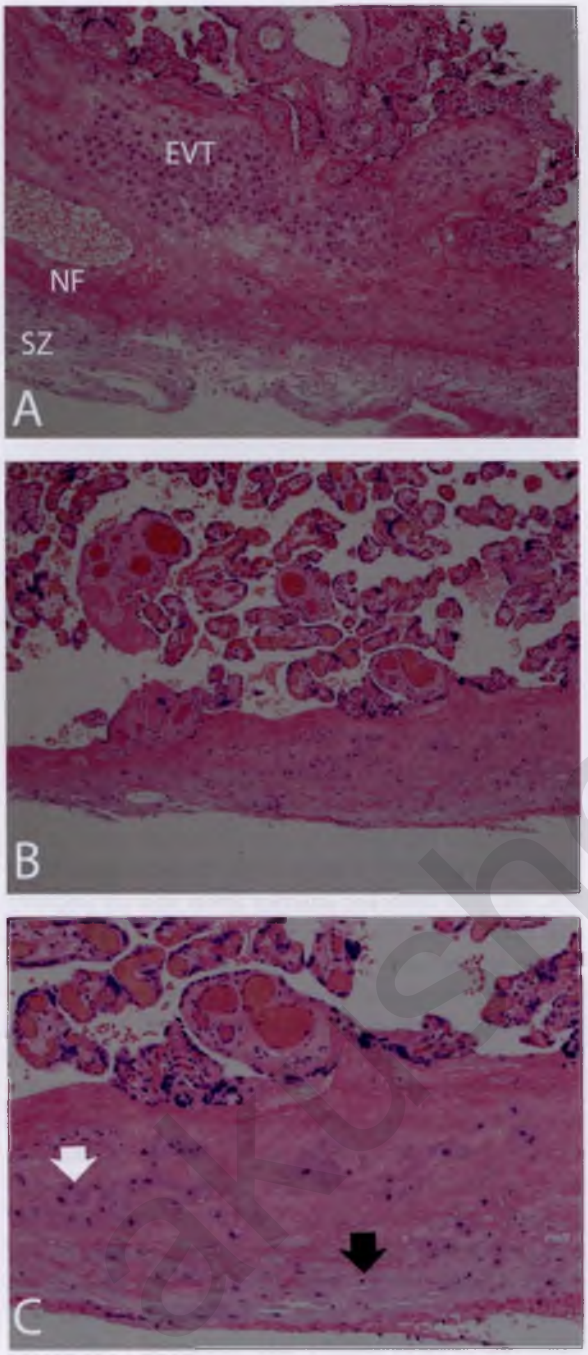

Figure 28.1 (a) Normal basal plate of the placenta. At the top of the image are the basal chorionic villi delimited by Rohr's fibrinoid layer. EVT can be seen in clusters adjacent to the anchoring villi. Nitabuch's fibrinoid layer (NF) delimits the separation zone (SZ) which in this case is composed mostly of decidua. EVT can be seen in the separation zone. (b) Basal plate from the same placenta with less well defined layers. (c) Basal plate to show the histologic differences between EVT (white arrow) and decidual cells (black arrow). These cells can be quite intermixed in the normal basal plate.

cells are normal constituents of the implantation site decidua and may play a role in controlling extravillous trophoblast cells (EVT) through cell surface interactions, cytokines, and growth factors. Other theories propose that abnormalities in the EVT lead to MAP; however, it remains controversial whether access to the deeper myometrial layers is the reason for abnormal deep trophoblastic invasion or whether MAP EVT are intrinsically more invasive. Detailed histologic analysis of hysterectomy specimens has revealed that EVT invade more deeply in MAP than in non-accreta cases, and that deeper myometrial vessel remodeling occurs in placenta increta and percreta[16]. However, accreta EVT do not have an increased proliferative index[16]. Interestingly, uterine vascular remodeling also appears abnormal in MAP with incomplete and sometimes absent remodeling seen in accreta cases, suggesting impaired trophoblast function[16]. A recent study has shown that EVT in accreta have no or reduced levels of E-cadherin expression by immunohistochemistry[25]. Lastly, there may be genetic contributions to MAP affecting decidualization or trophoblast invasiveness, as up to 18 percent of MAP occurs in nulliparous women without significant risk factors for accreta[9].

Gross Features: Several types of specimens may be submitted to pathology with findings in the spectrum of MAP, including D&C, delivered placenta (intact, disrupted, or fragmented), hysterectomy after placental delivery, and hysterectomy with placenta in situ. For all of these specimens, it is important to make note of the appearance of the junction between the placenta and uterus and sample the implantation site, even if the two organs are no longer in contact. It can be difficult to identify the ectocervical mucosa on these specimens due to cervical effacement, but sampling of the most inferior end of the specimen can help to clarify the extent of cervical removal.

Dilation and *Curettage*: Implantation site decidua, and even fragments of myometrium can be difficult to recognize grossly amongst the many tissue fragments in a D&C. Liberal sampling is suggested if there is a clinical suspicion of MAP.

Delivered Placenta: There are no specific gross features of MAP in a delivered placenta. A grossly apparent fragment of myometrium on the maternal surface of the delivered placenta is only rarely seen (Figure 28.2). Gross features suspicious for MAP may include focal or complete disruption of the maternal surface, absent cotyledons, or fragmentation of the

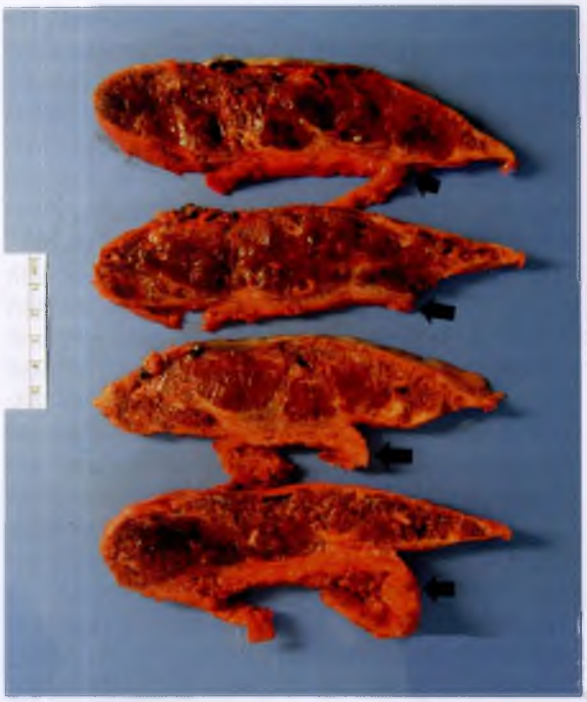

Figure 28.2 Serially sectioned placenta delivered with clinically suspected focal accreta. Chorionic surface is oriented at the top of each slice. Note the large fragment of tan tissue adherent to the basal surface (arrows), which histologically is myometrium with features diagnostic for accreta.

specimen. Adequate sampling of the junction between placenta and uterus – the basal plate – is the key to making a diagnosis of MAP in a delivered placenta. Areas of the maternal surface that contain "bare" parenchyma without intact basal plate do not have a high yield; however, multiple samples of the intact basal plate adjacent to the disrupted areas will increase the yield.

Hysterectomy after Placenta Delivery: MAP should be considered for any hysterectomy specimen received after placental delivery and removed for persistent postpartum bleeding. The postpartum uterus is universally enlarged. Photographic documentation of the anterior and posterior external surfaces is recommended. Notation of previous or recent cesarean scars should be made, as well as any therapeutic interventions for postpartum hemorrhage, such as B-lynch sutures. Upon opening of the uterus along the lateral aspects, the endometrial cavity may also be enlarged. The postpartum endometrial lining consists predominantly of decidua which can have a thickened, spongy red-pink, focally hemorrhagic, corrugated to rugated appearance (Figure 28.3). This appearance can make it

Figure 28.3 Postpartum hysterectomy specimen with hemorrhagic- and rugated-appearing endometrial surface.

difficult to distinguish between normal decidua and adherent placental tissue. In some cases, obvious placental tissue appearing as spongy red villous parenchyma is observed within the endometrial cavity, and this is the area from which samples for histology should concentrate (Figure 28.4). In other cases, when placental tissue is not obviously identified on gross examination, consultation of the medical record can be helpful to determine where the placenta was implanted. Liberal sampling of the endometrial cavity is suggested, concentrating in the suspected area of implantation. In the absence of definitive knowledge of the implantation site, sections from the anterior lower uterine segment are likely to increase the diagnostic yield for MAP. It may be necessary to revisit the specimen and submit additional samples after review of the first sections.

Hysterectomy specimen with placenta in situ: For cases of known placenta accreta/increta/percreta, a cesarean hysterectomy is typically performed. Since these specimens are rare and seen mostly in specialized centers, handling instructions are not easily found in most pathology grossing manuals. However, a detailed description by Dannheim et al.[26] provides an excellent review of these specimens. Consultation with the medical record and/or surgeon is recommended in these cases to clarify how invasive the placenta was observed to be at surgery and discuss any iatrogenic disruption to the specimen. The uterus is typically enlarged, and the most common scenario is implantation over the cervix (placenta previa) and/or in the anterior lower uterine segment, usually over a previous cesarean section scar. Therefore, the anterior lower uterine segment appears expanded and bulging (Figure 28.5). Sometimes just a thin layer of myometrium or serosa is visible over the bulging placental

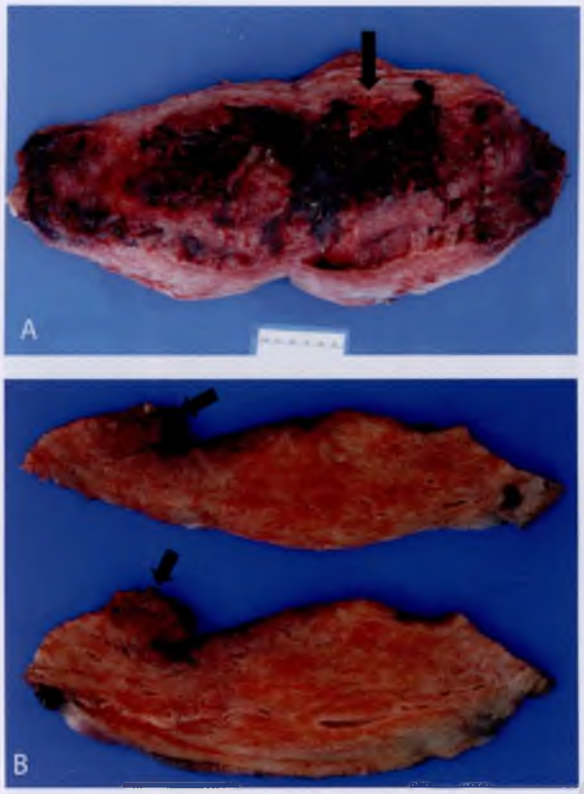

Figure 28.4 (a) Postpartum hysterectomy specimen after delivery of twins. The endometrial cavity shows focal hemorrhage and grossly recognizable placental tissue in the uterine fundus (arrow). (b) Cross sections of the uterine wall confirm the gross impression of placental tissue (arrows) extending into the superficial myometrium (placenta increta).

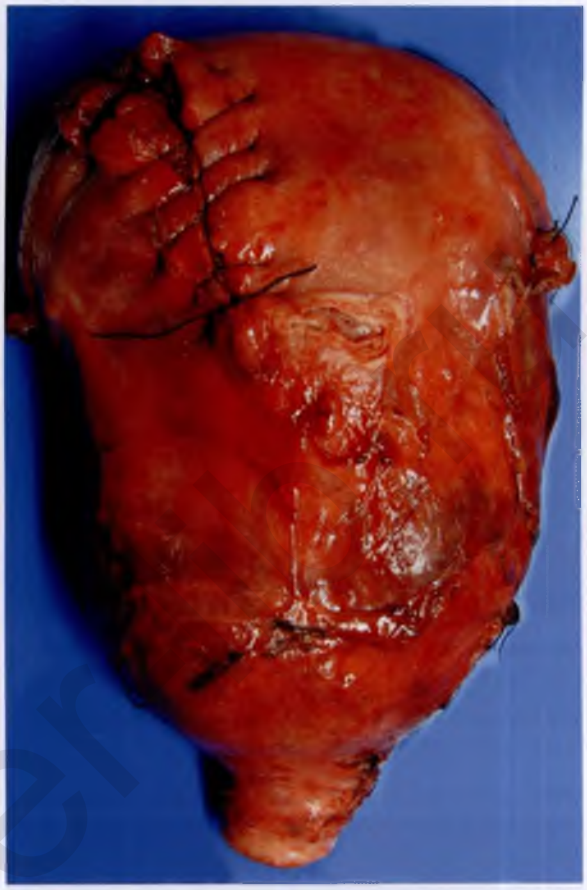

Figure 28.5 Cesarean hysterectomy specimen viewed anteriorly showing marked expansion of lower uterine segment indicating low-lying placental implantation. The external surface of the uterus in this case appears intact without evidence of full thickness penetration by placental tissue.

tissue in the lower uterine segment. Any disruption in the integrity of the uterine surface should be noted, as this could indicate placenta percreta versus iatrogenic disruption of the thin myometrial wall (Figure 28.6). After photographic documentation of the external surface, it can be helpful to ink the nonserosal tissues of the lower uterine segment and parametria. Technique to open the uterus may vary with the position of the placental implantation, but when there is implantation in the anterior lower uterine segment, a midline sagittal incision, along with parallel parasagittal incisions, can be an excellent way to evaluate the extent of the anterior uterine wall invasion (Figure 28.7). Sampling of the junction between the placenta and uterine wall are critical to define placenta accreta and determine the extent of disease. At least 4 sections of the uteroplacental interface are recommended[26], and should include the areas of deepest invasion and the transition from thickened to thinned myometrium. In addition to sampling the interface, samples of the placental parenchyma to include the chorionic surface and any parenchymal lesions, along with umbilical cord and samples of the membranes which are typically attached to the nonimplantation site uterine wall should be examined. Intervillous thrombi are frequently noted along the advancing edge of the placenta.

Microscopic Features: By definition, accreta is a histologic diagnosis, requiring that chorionic villi are implanted upon myometrium without intervening decidua. While some cases will show chorionic villi in direct contact with myometrium, and the diagnosis is straightforward, chorionic villi in accreta are frequently surrounded by fibrin and focal EVT. If this admixture of villi encased in fibrin and EVT is in direct contact with myometrium

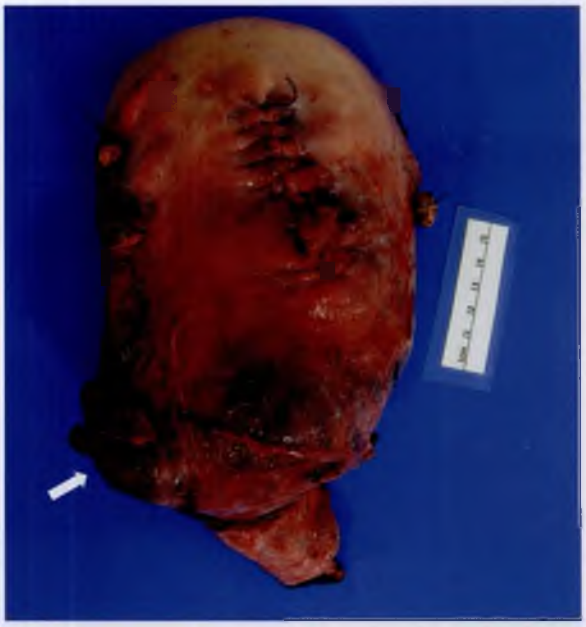

Figure 28.6 Cesarean hysterectomy specimen viewed anteriorly showing marked expansion of lower uterine segment. The anterior surface of the uterus is congested and shows a defect on the right side from which placenta protrudes (arrow), consistent with gross evidence of placenta percreta.

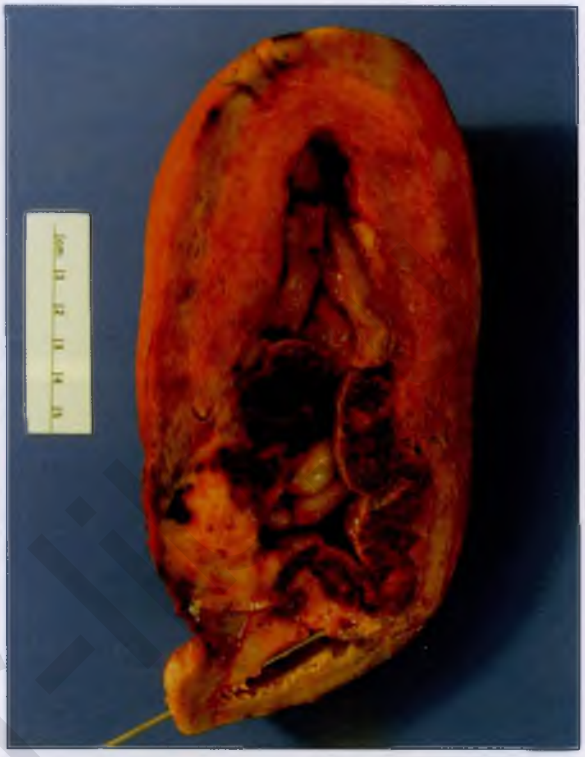

Figure 28.7 Cesarean hysterectomy specimen after midline sagittal incision. Note complete placenta previa with placenta covering the internal cervical os (probe in endocervix) and extension of the placental tissue into the myometrium of the lower uterine segment.

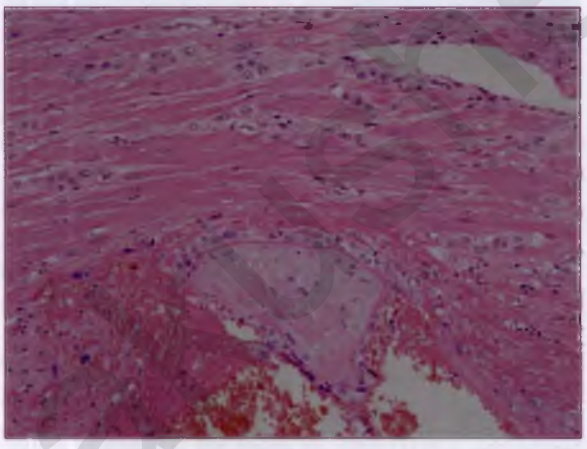

Figure 28.8 Histologic image from a hysterectomy specimen at the implantation site showing a chorionic villous surrounded by fibrin and EVT, implanted upon myometrium without intervening decidua, diagnostic for accreta.

without intervening decidua, a diagnosis of accreta can still be made (Figure 28.8). Difficulties can arise in the diagnosis of accreta for two reasons: (1) Decidual cells can be difficult to definitively identify, especially in a jumbled, disorganized implantation site, and (2) there are no practical definitions of the thickness of the normal decidual layer so the meaning of a subjectively thin layer of decidual tissue between chorionic villi and myometrium is unclear. Decidual cells are distinguished by their pale polygonal shape and eosinophilic to gray cytoplasm compared to the more amphophilic cytoplasm of EVT (Figure 28.9). Currently, cases with what appears to be a thin layer of decidua (felt to be "inadequate" decidualization) do not meet the criteria for a diagnosis of accreta. In these circumstances when a specimen has been adequately sampled, use of the diagnosis "changes suggestive of placenta accreta" with description of the thin layer of basal decidua may be appropriate.

The histologic definition of accreta does not mention the presence/absence or position of EVT. EVT are resident in the basal plate and infiltrate both the decidual tissue and the myometrium in normal pregnancy. Deeper invasion of the uterine wall by EVT has been reported in cases with increta and percreta, as well as deeper vascular remodeling of

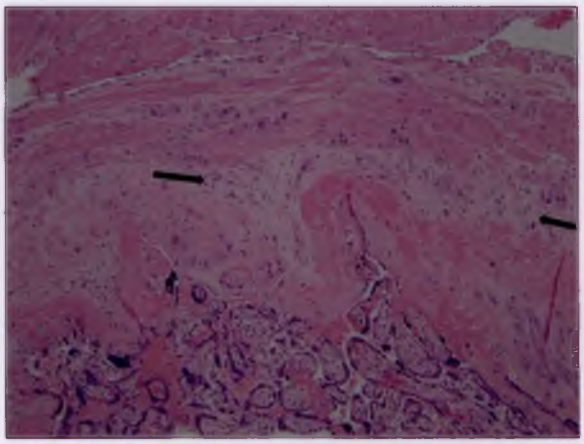

Figure 28.9 Histologic image from a hysterectomy specimen at the implantation site showing chorionic villi separated from the myometrium by a thin layer of tissue (between arrows). It can be difficult to determine the cellular composition of the intervening tissue, and decide if decidua is present. In this case, other areas showed more convincing areas diagnostic for accreta. Image provided with permission by L. Ernst, Northshore University Healthsystem, Evanston, IL.

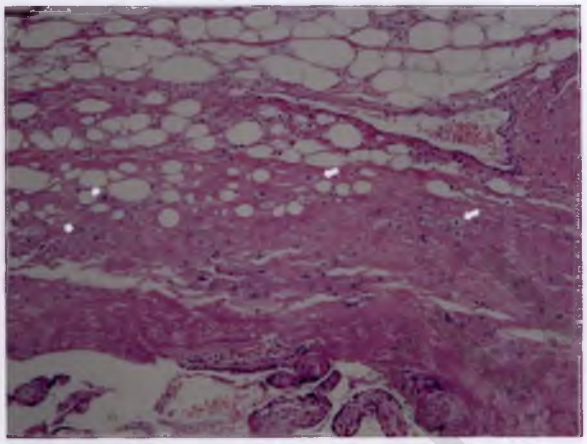

Figure 28.10 Histologic image from a hysterectomy specimen with placenta percreta showing chorionic villi/implantation site (lower border) invading through the uterine wall with complete lack of myometrium. EVT are seen percolating through the adherent fat (arrows).

large outer myometrial vessels[16]. However, the presence of EVT in the myometrium cannot be used as definitive evidence of accreta. Some have stated that EVT in the myometrium not focused on vessels may indicate abnormal trophoblast invasion[26], and others have suggested that intrusion of venous vessels by chorionic villi and increased numbers of proliferative EVT can assist in the histologic diagnosis of MAP[27]. Placenta percreta can be confirmed histologically when chorionic villi are seen next to adipocytes[26] (Figure 28.10) or a portion of bladder wall. Ink on chorionic villi can indicate extension to the external margin without myometrium present. Additional histologic placental findings reported in association with MAP include increased trophoblast stromal inclusions[28], findings of maternal vascular malperfusion, evidence of chronic intrauterine bleeding, and chronic inflammation at the implantation site[29].

Ancillary Diagnostic Testing: Pathologic diagnosis of the MAP relies on H&E assessment. CD10 immunohistochemistry has been reported to be of value in delineating decidual cells[26]. Cytokeratin stains can be used to highlight EVT.

Prognostic Implications: The need for hysterectomy in severe cases of MAP has an obvious negative impact on future fertility. When the uterus can be preserved, a diagnosis of MAP in a previous pregnancy carries a risk of recurrent MAP in the next pregnancy and the possibility of more advanced disease[3,4].

Knowledge Gaps: *Terminology and definitions*: With the increasing incidence of MAP, the pathologist is likely to encounter specimens in the MAP spectrum of disease. A pathology consensus statement and potentially an expansion of the diagnostic criteria for MAP would be helpful. *Serum markers of accreta,* such as cell free placental mRNA in maternal plasma[30] and vascular endothelial growth factor[31] are beginning to be investigated. *Endometrial regeneration*: Proper decidualization requires an intact endometrium. Studies have shown that endometrial-like epithelium can be generated from human embryonic stem cells, but the use of stem cells in the regeneration of reproductive tissues, such as scarred endometrium, is still under investigation [22]. *Pathogenesis*: The pathogenesis of MAP remains controversial and methods to improve decidualization and/or control EVT invasiveness are still lacking. Investigations into epithelial-to-mesenchymal transitions in EVT suggest that EVT differentiation plays a role in EVT invasiveness[31,32]. Most accretas are associated with uterine scarring from previous cesarean sections, but criteria to distinguish between dehiscence of a uterine scar leading to exposed placenta and truly abnormal implantation are lacking. Further pathologic study of hysterectomy specimens may provide insights into pathogenesis.

Adherent Myometrial Fibers on Basal Plate (Basal Plate Myofibers, Smooth Muscle Cells within Basal Plate, "Occult Placenta Accreta," BPMYO)

Definition: Myometrial fibers adherent to the basal plate (BPMYO) is a histologic finding in the delivered placenta[1–5] and represents a lesion in the spectrum of MAP because normal placental separation should occur at the basal decidual separation zone without removal of myometrium. As described above, attached myometrium with diagnostic changes of placenta accreta may be seen in the delivered placenta, but not all placentas with adherent myometrial fibers show diagnostic changes of accreta. The majority of placentas with adherent myometrial fibers show the presence of a variably thick layer of basal decidua, ranging from normal to thin. Even when not diagnostic for accreta, the presence of BPMYO should be noted since there are potential prognostic implications (see below).

Clinical Context: The incidence BPMYO is not certain, but it has been reported in more than 40 percent of placentas submitted to pathology without any clinical suspicion of MAP[3]. The extent and location of the samples of the basal plate examined may affect the incidence of BPMYO[5]. Additionally, BPMYO has been reported more commonly in preterm than term births[2].

Proposed Pathogenesis: The pathogenesis of BPMYO is not certain, but abnormally deep trophoblastic invasion has been postulated as a cause[2]. The pathogenesis of BPMYO may parallel the pathogenesis of accreta.

Microscopic Features: The normal basal plate is an intimate mixture of both maternal and fetal tissue bound by a lining of syncytiotrophoblast cells and Rohr's fibrinoid on the fetal side[33]. The histologic features of the basal plate are shown in Figure 28.1. Myometrial cells are not considered a normal component of the basal plate, but can be identified in pathologic samples of the basal plate (Figure 28.11). In the most superficial form of BPMYO, myometrial fibers are seen on the separation zone side of the basal plate with other components of the basal plate intact[3,4]. In some cases, the decidual layer between chorionic villi and myometrium is still present, but reduced in thickness to just few cells. When the decidual layer is reduced to two cell layers or less, this has been called

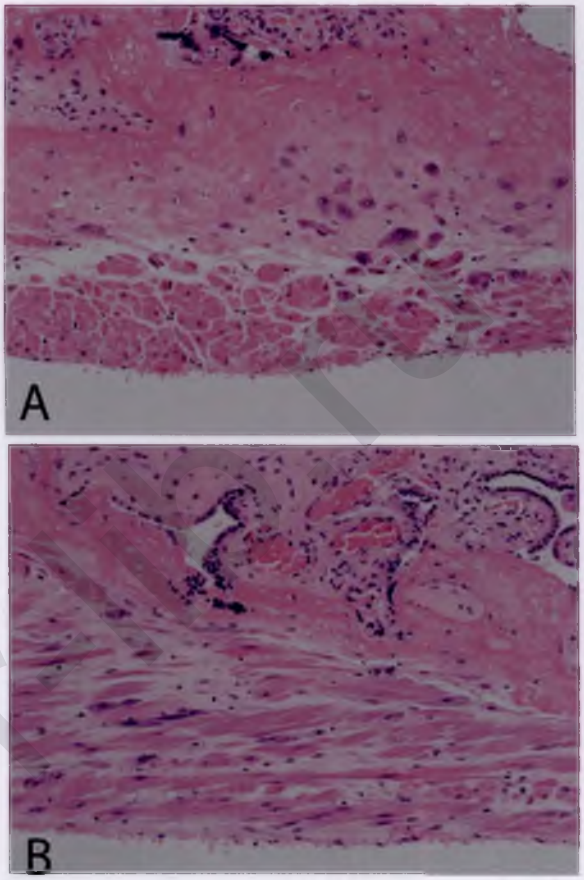

Figure 28.11 Histologic images of the basal plate of placenta with adherent myometrial fibers which appear as closely approximated, polygonal cells with eosinophilic cytoplasm and central boxy to rectangular nuclei. (a) cross sections of myofibers,(b) longitudinal sections of myofibers. Image provided with permission by L. Ernst, Northshore University Healthsystem, Evanston, IL.

"changes suggestive of focal accreta"[3]. Finally, in some cases, diagnostic accreta can be seen on the basal plate characterized by complete lack of decidua between the myometrial fibers and the basal chorionic villi and/or Rohr's fibrinoid. The same principles and pitfalls regarding accreta diagnosis apply in the delivered placenta. Associated placental pathologic findings include decreased placental weight, evidence of intrauterine bleeding, findings of maternal vascular malperfusion and chronic basal inflammation[2,29]

Prognostic Implications: Case-control studies have shown the presence of BPMYO portends a risk of developing MAP in a subsequent pregnancy[3,4]. The risk is greater when the decidua separating the myometrial fibers from chorionic villi or Rohr's

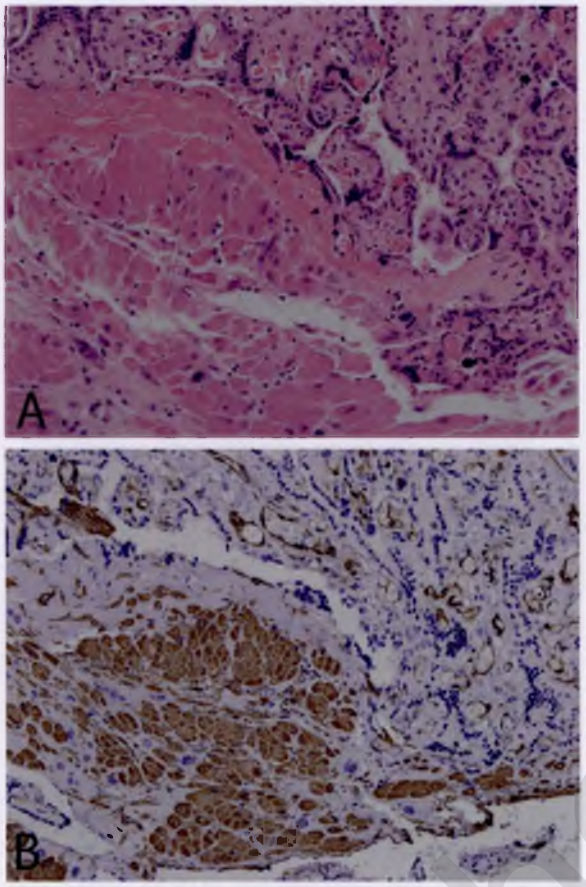

Figure 28.12 Histologic images of the basal plate of placenta with adherent myometrial fibers in continuity with Rohr's fibrinoid diagnostic for accreta. (a) (H&E 200x). (b) (Immunostain: smooth muscle actin).

fibrinoid is ≤2 layers thick, or when there is a large quantity of attached myometrium[3]. It has been shown that adding BPMYO to an algorithm can help to predict the risk of subsequent MAP[4].

Knowledge Gaps: *Terminology:* The Amsterdam consensus did not address terminology for the lesions within the MAP spectrum, and universal terminology would be beneficial. *Mode and type of delivery:* It is unclear if mode of delivery (cesarean section versus vaginal delivery versus manual extraction) or type of gestation (twin versus singleton) has any effect on the incidence of BPMYO.

Cesarean Scar Pregnancy (Isthmocele Pregnancy)

Definition: Cesarean scar pregnancy (CSP) is a rare form of ectopic pregnancy in which implantation occurs at the site of a previous cesarean section scar and, therefore, can be considered an iatrogenic complication of cesarean section.

Clinical Context: The estimated incidence of CSP is 1/1688 – 1/2216 pregnancies[34], and some suspect that in countries with the increasing rate of cesarean section, the incidence of CSP is expected to rise[34]. Diagnosis is made on prenatal sonogram with implantation of the gestational sac noted into a cesarean delivery scar[12]. Major complications associated with CSP include uterine rupture, life-threatening hemorrhage, and need for hysterectomy. While some cases of successful livebirth with CSP have been reported[6], the majority of cases are managed by termination of the pregnancy. Conservative options include systemic methotrexate, uterine artery embolization, local resection, operative hysteroscopy, and uterine suction curettage[34].

Proposed Pathogenesis: The pathogenesis of CSP is likely multifactorial. Risk factors that have been recognized include multiple previous uterine surgeries, such as cesarean section or myomectomy, and a brief interval between the surgery and the subsequent pregnancy[35]. A study in China found that recurrent CSP was significantly increased with a history of previous cesarean section at a rural community hospital. These findings suggest surgical technique may influence uterine incision healing[35]. Other factors that increased the risk of recurrent cesarean pregnancy were a thinner lower uterine segment (<5 mm)[35]. The effect of a cesarean section scar on the uterine microenvironment is not well understood. However, one prospective case-control study showed that a cesarean section has a significant effect on the site of placental implantation in subsequent pregnancies with an increased incidence of posterior, nonfundal implantations after cesarean section compared with controls[36]. While this observation does not necessarily explain why an anterior cesarean section scar might attract the implanting blastocyst, it does suggest that cesarean section scars can have a widespread impact on the endometrium and myometrium.

Gross Features: Pathologic specimens of CSP are rare, but when hysterectomy is required, a gestational sac is typically found in the lower uterine segment with placental implantation upon a thinned, scarred anterior myometrial wall (Figure 28.13).

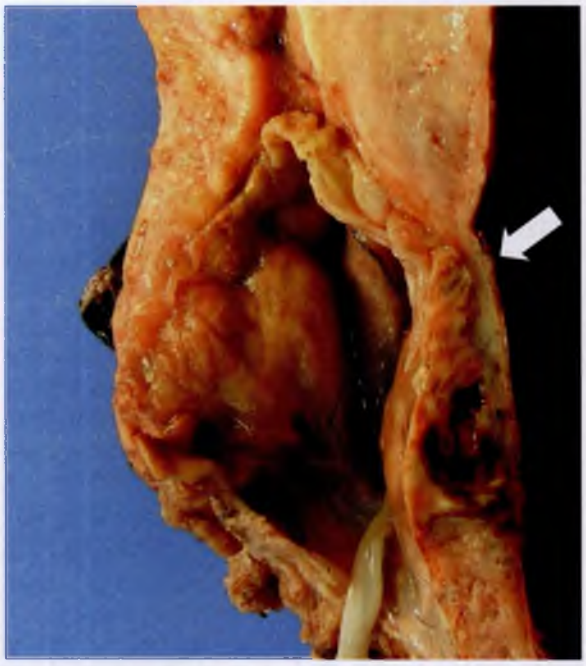

Figure 28.13 Cesarean scar pregnancy status post-hysterectomy at 13 weeks gestation to a women with 4 previous cesarean sections and failed medical termination of pregnancy earlier in gestation. Note the thinned and scarred myometrium at the implantation site (arrow). The gestational sac extends to the posterior uterine wall. Image provided with permission by L. Ernst, Northshore University Healthsystem, Evanston, IL.

Microscopic Features: CSP may show evidence of accreta and/or chorionic villi implanted on fibrotic, scarred myometrium (Figure 28.14).

Prognostic Implications: CSP can have a negative impact on future reproductive potential. Subsequent conception is achievable in most women (87.5 percent) who did not require hysterectomy, and outcomes in a small case series (N=8) have included a normal term pregnancy (62.5 percent), miscarriage (25 percent), recurrent CSP (11 percent), and placenta accreta (20 percent). Diverticulum or defect in the lower uterine segment was also been reported[37]. Elective repeat cesarean section is the preferred mode of delivery for pregnancies following CSP.

Knowledge Gaps: A better understanding of the mechanisms that determine site of implantation, and methods to improve surgical technique and healing after cesarean section could reduce the incidence of CSP.

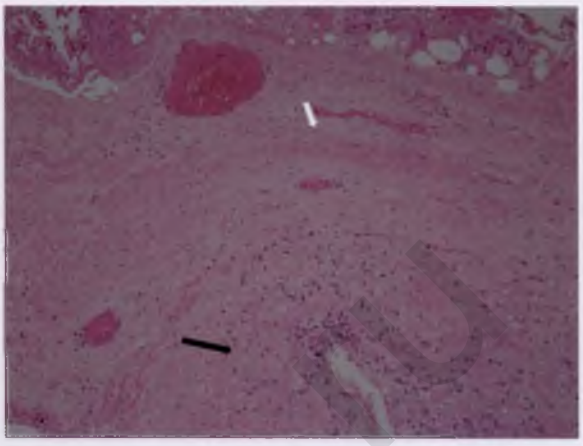

Figure 28.14 Histologic section from the thinned area of myometrium in cesarean scar pregnancy showing replacement of myometrial fibers with wavy collagen fibers (white arrow). Black arrow indicates the edge of the implantation site.

Retained Placenta (Fragmented (?Incomplete) Placenta, Retained Products of Conception, Adherent Membranes, Retained Membranes)

Also see Chapter 30 for a discussion of the retained products of conception in the context of postpartum hemorrhage

Definition: Retained products of conception (POC) refers to any gestational tissue that remains in the uterus after operative delivery, vaginal delivery or termination of pregnancy. In the setting of active management of labor, retained placenta is defined as a placenta that has not separated from the uterus within 30 mins of delivery of the fetus. A retained placenta does not necessarily lead to retained POC.

Clinical Context: Retained POC is reported in nearly 1 percent of pregnancies[38], and retained placenta is noted in approximately 3 percent of all deliveries[39]. Retained POC is more common after termination of pregnancy and midtrimester deliveries[38]. Retained POC presents with vaginal bleeding and pain beyond that normally expected. Pelvic sonography can be used as an assessment tool and is used to determine the thickness of the endometrial echo complex. Abnormal findings include a thickened and vascular endometrial echocomplex or echogenic material within the endometrial canal[38]. Treatment for retained POC includes misoprostol, hysteroscopy, and D&C. Retained placenta after delivery of the

infant may require a simple manual removal of the placenta, manual extraction in multiple pieces, D&C, or hysterectomy.

Proposed Pathogenesis: The exact mechanisms of normal placental separation are poorly understood and therefore the reasons for delayed placental separation are unclear. Associations with preeclampsia, preterm birth, intrauterine growth restriction, and recurrent miscarriages have been reported with retained placenta[39], suggesting a link to defective placentation. However, pathogenic mechanisms have not been fully elucidated. A relationship between retained placenta and accreta is seen in some, but not all cases.

In some cases anatomic considerations such as an accessory lobe or bilobed placenta may be the cause of retained placenta.

Gross Features: Retained POC are generally fragmented specimens composed of fragments obtained at D&C including villous tissue, decidua, endometrium, and myometrium. When examining any placenta the completeness of the maternal surface should be evaluated to determine if portions of the placenta were not completely removed. Clues to incomplete removal may include focal raggedness of the maternal surface, missing cotyledon, partial accessory lobes, and fragmentation with placental weight small for gestational age. A study of term retained placentas noted that the retained placentas have a smaller surface area and more oblong shape[39].

Microscopic Features: The appearance of retained POC varies with duration of retention in utero. The villous changes include involution of the villous vasculature similar to those seen in stillbirth, villous fibrosis, collapse of the intervillous space, increased perivillous fibrin deposition, and dystrophic calcification (Figure 28.15). There may also be portions of membranes present and segments of implantation site. Inflammation, clot, decidua, and myometrium may also be present. At term, retained placentas have been shown to have more findings of maternal vascular malperfusion and increased incidence of adherent basal plate myometrial fibers[39]. Diagnostic accreta should be excluded.

Prognostic Implications: The main complications of retained POC are infection and hemorrhage.

Knowledge Gaps: A better understanding of the mechanisms that control placental separation in both normal and abnormal pregnancies may help advance the management of retained placenta.

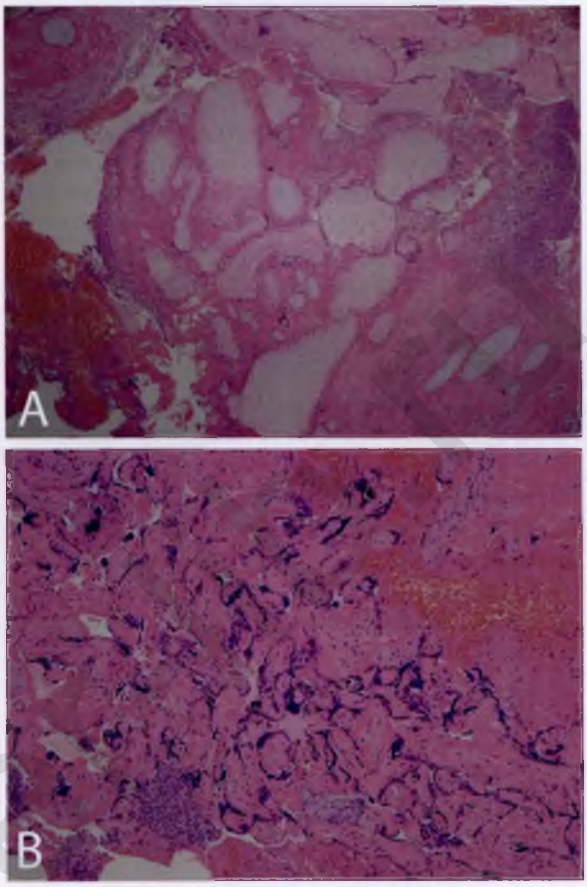

Figure 28.15 (a) Image from a D&C for retained POC. Chorionic villi are collapsed on one another with increased perivillous fibrin deposition. Villous vasculature is involuted, but the stroma is not fibrotic yet. Associated inflammation is present. (b) Retained POC specimen with more villous fibrosis, indicating longer retention in utero.

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Chapter 29

Uterine Rupture/Dehiscence

Sydney Card and Ann Folkins

Uterine Rupture (Complete Rupture), Uterine Dehiscence (Partial Rupture)

Definition: Uterine rupture describes a complete, full-thickness rupture of the uterine wall; uterine dehiscence describes a partial rupture of the uterine wall with an intact uterine serosa.

Clinical Context: In a resource-rich practice setting, complete uterine rupture usually occurs in the context of a scarred uterus, with the majority of cases occurring in patients with a history of cesarean section (Table 29.1). The estimated incidence of uterine rupture in the setting of trial of labor after cesarean section (TOLAC) in the United States is less than 1 percent (32.5–70 per 10,000 trials of labor after cesarean)[1,2]. Among these patients, those with classical and low-vertical cesarean section scars, as well as women who undergo labor at term, have a higher risk of rupture[1,3]. Because they have similar risk factors (prior uterine scarring, grand multiparity, etc.), an association between placenta creta and uterine rupture has been described in several case reports in the literature[4–6]. Uterine rupture in an unscarred uterus is much less common in resource-rich practice settings (1–2 per 10,000 deliveries in the United States) and relatively more common in resource-poor areas[7,8].

Complete uterine rupture has a nonspecific clinical presentation; symptoms may include abdominal pain, vaginal bleeding, maternal tachycardia, and nonreassuring fetal heart rate. The difficulty in diagnosis is due to the fact that these symptoms may be seen in normal nonruptured labor, or in nonruptured labor with other complications (e.g. cephalopelvic disproportion, perineal or vaginal tear, etc.). A high clinical index of suspicion is required for making the diagnosis. The rupture may be visualized with ultrasound or seen intraoperatively during an emergency cesarean section performed for maternal or fetal distress[7,8]. Partial uterine rupture is usually clinically occult and discovered incidentally during surgery or antepartum ultrasound imaging[9].

Table 29.1 Risk factors for uterine rupture

Iatrogenic	Previous cesarean section or other uterine surgery
	Oxytocin use
	Misoprostol use
	Obstetrical version maneuvers
Maternal	Prior uterine rupture
	Cephalopelvic disproportion
	Grand multiparity
	Uterine structural abnormalities
	Connective tissue disorders
Fetal	Macrosomia
	Malpresentation
	Shoulder dystocia
Other	Trauma

Risk factors for uterine rupture in both scarred and unscarred uteri include trauma (e.g. motor vehicle collisions), imprudent use of oxytocin in labor induction or augmentation, labor induction with misoprostol, prior uterine rupture, maternal connective tissue disorder (e.g. type IV Ehlers-Danlos syndrome), grand multiparity, uterine structural abnormalities, cephalopelvic disproportion, obstetric version maneuvers, fetal macrosomia, shoulder dystocia, and malpresentation (Table 29.1)[1,8,10–14]. Uterine rupture in resource-poor settings is often related to obstructed labor due to mechanical factors (cephalopelvic disproportion, malpresentation, grand multiparity), with a lack of available operative delivery[15].

Proposed Pathogenesis: In cases with a prior cesarean section, rupture is attributed to residual weakness

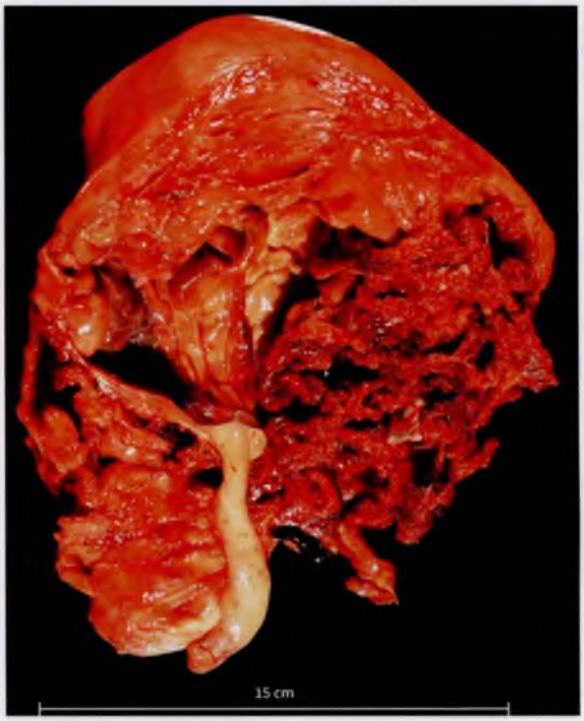

Figure 29.1 Hysterectomy with complete uterine rupture. Placental tissue is protruding from the rupture site in the anterior lower uterine segment.
Image courtesy of Drucilla Roberts, Massachusetts General Hospital.

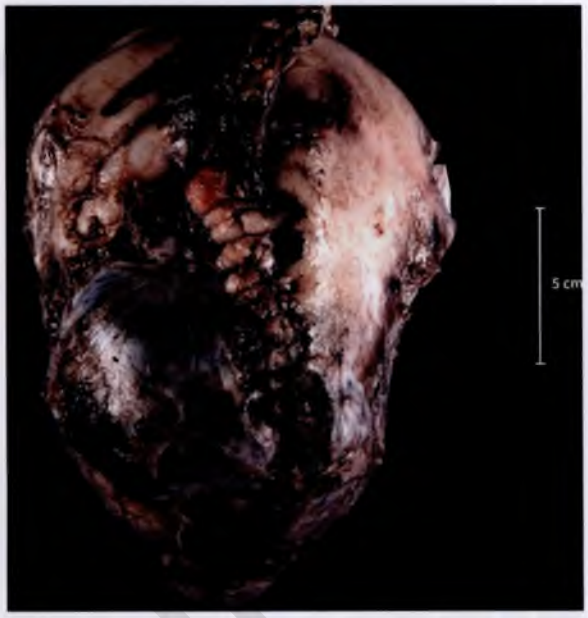

Figure 29.2 Hysterectomy with placenta percreta in the anterior lower uterine segment and rupture in the right lateral aspect.

in the uterine wall after scarring, often with superimposed factors. In the unscarred uterus, intrinsic (structural anomalies in the uterus, connective tissue disorders) or acquired (grand multiparity) factors may weaken the uterine wall and predispose to rupture. Scarred and unscarred uteri may be affected by mechanical factors (cephalopelvic disproportion, shoulder dystocia) and labor management practices such as prostaglandin and oxytocin use. In rare cases of type IV Ehlers-Danlos syndrome (vascular type) a mutation in *COL3A1* causes defective synthesis of type III procollagen, producing an intrinsic connective tissue weakness that makes muscular arteries and hollow viscera especially prone to rupture[16].

Gross Features: When the rupture is repaired and no hysterectomy is performed, the placenta may be fragmented due to mechanical disruption. The placenta may be submitted *in situ* if the rupture results in a hysterectomy (Figure 29.1). In these cases, there may evidence of an attempt to surgically repair the rupture prior to hysterectomy. The placenta may be grossly adherent to the uterine wall if there is placenta accreta or present at the serosal surface if there is placenta percreta (Figure 29.2). Gross photographs of the rupture site and careful documentation of surgical interventions should be performed in all hysterectomy cases.

Microscopic Features: The placenta does not show specific intrinsic anomalies but may be associated with significant adherent blood and fibrin. Fragmentation may result in artificial tracking of the villi along clefts in myometrium. The myometrium in the area of the rupture will show hemorrhage, usually with minimal organization. A careful search should be made for evidence of placenta creta (accreta, increta, or percreta), as this is commonly encountered in the same clinical context.

Ancillary Diagnostic Testing: A Masson trichrome stain may aid in identifying subtle uterine scarring, but this is not typically necessary. In cases clinically suspicious for Ehlers-Danlos syndrome, vascular type (type IV), fibroblast culture or peripheral blood testing can identify germline mutations in *COL3A1*[16].

Prognostic Implications: The most common maternal morbidities related to uterine rupture are postpartum hemorrhage, need for transfusion, and hysterectomy[17].

Ruptures that occur in an unscarred uterus are associated with significantly more morbidity, including higher rates of transfusion and hysterectomy, worse neonatal neurologic outcomes, and perinatal deaths[11,18]. This is thought to be related to closer observation in patients with a history of cesarean section, where obstetricians have a much higher suspicion for uterine rupture and ensure rapid operative delivery is available. Partial uterine rupture is associated with minimal/no maternal or fetal morbidity or mortality[9].

In resource-rich practice areas, maternal mortality ranges from 0–0.2 percent [North American data] with a perinatal mortality rate of approximately 5 percent[1,19,20]. Fetal/perinatal morbidity is often related to intrauterine hypoxia and includes low Apgar scores, intraventricular hemorrhage, periventricular leukomalacia, and seizures[11,13]. One US study found that 6 percent of infants developed hypoxic ischemic encephalopathy after uterine rupture[2]. In resource-poor practice settings, maternal and fetal morbidity and mortality are significantly higher due to lack of antenatal care, trained birth attendants, and available emergency obstetrical services[15]. Factors contributing to maternal and fetal death can also be categorized according to the three-delay model[21]. This refers to delay in seeking care, delay in arriving for care, and delay in receiving appropriate care.

Knowledge Gaps: No method currently exists to predict uterine rupture. In patients with a history of cesarean section, prenatal care by obstetricians with expertise in high-risk pregnancies and delivery in a tertiary center has helped to ensure good outcomes for mother and fetus.

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Chapter

30

Postpartum Hemorrhage

Koah Vierkoetter and Ann Folkins

Postpartum hemorrhage (PPH) is defined as hemorrhage greater than 500 mL following vaginal delivery or bleeding greater than 1000 mL after cesarean section[1]. As accurate quantification of blood loss may prove clinically difficult[2], alternate definitions have been proposed, including a decrease in hematocrit of >10 percent[1], active bleeding despite initial management attempts[3], necessity for red blood cell transfusion[4], or need for postpartum hysterectomy[5,6]. Clinically, PPH is further described as primary (or early) and secondary (or late), with early PPH occurring within 24 hours of delivery and late PPH between 24 hours to 6 weeks after delivery[1].

Overall, the incidence of PPH following live birth is estimated at 1–6 percent[1,7,8]. In recent years, the incidence of PPH appears to be rising[9,10]. The underlying causes of PPH may be characterized as attributable to the "four T's" – tone (uterine atony), trauma (lacerations, inversion, etc.), tissue (retained products of conception), and thrombin (preexisting or acquired coagulopathy)[11]. Etiologies of PPH may also be categorized temporally (see Table 30.1)[12]. Several of these processes are discussed in depth in other chapters. This chapter discusses the clinical and placental findings observed in (a) uterine atony, (b) subinvolution of the placental site, and (c) retained placenta. PPH is a significant cause of maternal morbidity and mortality[12,13]. This is particularly true in developing countries, where PPH is a leading cause of morbidity, accounting for greater than 30 percent of maternal deaths in Africa and Asia[14].

Uterine Atony

Definition: Decreased contractility and loss of tone in the uterine musculature due to failure of the uterus to contract adequately following delivery[25].

Clinical Context: Atony is the most common cause of PPH, and is responsible for approximately 79 percent of cases of PPH and 34 percent of postpartum hysterectomies[1,12,26]. In a large sample of patients undergoing hysterectomy, 6 percent required administration of uterotonic agents to control hemorrhage due to atony[27]. The incidence of uterine atony has increased in recent years[9,12]. Clinical risk factors for uterine atony include those associated with uterine overdistension (fetal macrosomia, multiple gestations, polyhydramnios), abnormal labor (induction of labor, prolonged or precipitous labor), medications (uterine relaxants, tocolytics, terbutaline, magnesium sulfate, general anesthesia), and clinical findings suggestive of chorioamnionitis[25–28].

Proposed Pathogenesis: Immediately after delivery, appropriate uterine involution and hemostasis requires prompt contraction of the myometrium with constriction of denuded maternal blood vessels following placental separation[29]. Although both uterine and placental inflammation appear related to ineffective myometrial contractility, the exact mechanism is yet to be elucidated. While correlations with the risk factors listed above have been demonstrated, in a large proportion of uterine atony cases there is no known risk factor[27].

Gross Features: Soft, poorly contracted, "boggy" uterus with an enlarged endometrial cavity and thinned myometrium (Figure 30.1).

Microscopic Features: The myometrium is often edematous and hemorrhagic with markedly dilated uterine vessels. Histologic evidence of placental inflammatory lesions such as chorioamnionitis, umbilical cord vasculitis, chorionic plate vasculitis, and funisitis are significantly more common in postpartum hysterectomy specimens with clinical diagnosis of atony compared to non-atony controls[26]. Uterine inflammation (acute endomyometritis and cervicitis) is also significantly associated with uterine atony[26].

Ancillary Diagnostic Testing: No relevant ancillary diagnostic testing.

Table 30.1 Etiologies of postpartum hemorrhage (PPH)[12,15,16]

Etiology	Associated lesions and risk factors
Early PPH	
Uterine atony	• Uterine relaxation (tocolytics, terbutaline, magnesium sulfate, general anesthesia) • Placental inflammatory lesions (chorioamnionitis, meconium)
Infection	• Chorioamnionitis • Myometrial abscess or necrosis • Acute endomyometritis • Chronic endomyometritis
Coagulopathies	• Bleeding diathesis (acquired and inherited) • Disseminated intravascular coagulopathy • Amniotic fluid embolus • Thrombocytopenia
Lacerations	• Lacerations of the lower genital tract (instrumented or uncontrolled vaginal delivery) • Hysterotomy extension at cesarean section
Uterine rupture	• Scarred uteri (prior incision, curettage) • Overstimulation (oxytocin, misoprostol)
Abnormal placentation	• Placenta previa[17] • Morbidly adherent placenta • Abnormal implantation site
Uterine inversion	• Morbidly adherent placenta • Short umbilical cord • Fundal placental implantation • Excessive cord traction • Manual removal of placenta
Prolonged obstructed labor	• Malpresentation
Early or Late PPH	
Retained placenta	• Accessory lobe or bilobate placenta • Placenta adherens • Trapped placenta • Uterine anomalies
Morbidly adherent placenta	• Placenta accreta, increta, and percreta • Exaggerated placental site
Late PPH	
Subinvolution of placental site	• Retained products of conception
Infectious endometritis	• Chronic endomyometritis • Myometrial abscess
Persistence of implantation site trophoblast[18]	• Placental site nodule • Exaggerated placental site[19]
Choriocarcinoma[20]	• Molar or normal pregnancy
Leiomyoma[21–23]	• Submucosal/intracavitary lesion
Uterine pseudoaneurysm[24]	• Vascular injury at cesarean delivery

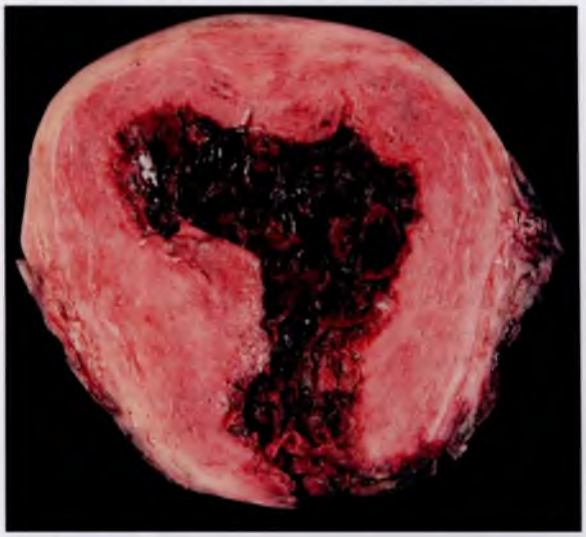

Figure 30.1 Postpartum hysterectomy from a patient with early PPH secondary to uterine atony. The uterine walls are boggy and soft, although not thinned. The endometrial cavity is distended with clotted blood. Acute endomyometritis was present on microscopic sections.

Prognostic implications: Although a number of effective, conservative interventions allowing for preservation of fertility for PPH due to atony exist (uterotonics, hemostatic drugs, radiological embolization, compression devices)[30], uterine atony remains a leading indication of emergent postpartum hysterectomy[31]. Notably, postoperative maternal complications occur in up to 44 percent of cesarean hysterectomies[32,33].

Knowledge Gaps: The pathophysiologic link between inflammation and the development of uterine atony is not well understood, and is an area for future study.

Retained Placenta

Definition: Intrauterine retention of placental parenchyma and/or membranes following delivery[34].

Clinical Context: Up to 3.3 percent of vaginal deliveries are complicated by retained products of conception[34], with lower rates in developing countries[35]. Hemorrhage secondary to retained placenta may occur either early or late. In the immediate postpartum setting, retained placenta should be considered in addition to uterine atony. In such cases, manual removal or curettage may be necessary. Ultrasonography may be used as an adjunct to the diagnosis, which displays a thickened endometrial echo or a discrete mass with demonstrable vascularity[36]. In pathologic specimens from late postpartum hemorrhage, retained placental fragments are the most common histologic finding (45 of 169 cases)[37]. Retained placental fragments are associated with higher rates of preeclampsia, history of previous cesarean section, maternal age >30 years, fetal growth restriction, spontaneous abortion, stillbirth, and spontaneous preterm birth[37–40].

Proposed Pathogenesis: Placental retention and ensuing PPH may be due to adherent placental tissue, which encompasses a spectrum from placenta adherens to placenta creta[41]. Placenta adherens refers to inadequate myometrial contraction for release of placental tissue. Placenta creta describes the spectrum of morbidly adherent placental disorders associated with implantation directly onto (accreta), into (increta), or through (percreta) the myometrium (see Chapter 28).

In other cases of retained placenta, there may be anatomic or iatrogenic causes. The placenta may become trapped behind a closed cervix. Placentas with structural abnormalities, such as a succenturiate lobe or bilobate placenta, are at increased risk for retention. Uterine anomalies, including septate or bicornuate uteri, as well as abnormal implantation, such as angular pregnancy, are associated with retained placenta[42]. Prolonged use of oxytocin during labor is a risk factor for retained placenta[43].

Gross Features: When compared to nonretained placentas, retained placentas exhibit a significantly smaller surface area and are more oblong in shape[44]. The retained products may form polypoid intrauterine mass (placental polyp). The maternal surface of the placenta is usually disrupted and ragged, at least focally. An attempt should be made to determine whether there are any missing cotyledons when examining the placenta grossly. Samples for microscopic examination should be taken at the junction of intact to disrupted maternal surface to best maximize the possibility of detecting microscopic placenta accreta[45].

Microscopic Features: Histological features of maternal underperfusion, including arteriopathy, infarction, accelerated villous maturation, fibrotic villi, and placental septal cysts, are significantly increased in retained placentas[44]. Sometimes the villi are necrotic, with smudgy nuclear chromatin and stromal karyorrhexis, with increased intervillous fibrin deposition. Absence of decidua between the placental implantation and uterine smooth muscle fibers is diagnostic of placenta accreta.

Ancillary Diagnostic Testing: No relevant ancillary diagnostic testing.

Prognostic Implications: Patients with a history of previous placental retention are at increased risk for retention in future pregnancies[37,43,46]. Antenatal diagnosis of a morbidly adherent placenta allows for delivery planning, which often involves cesarean hysterectomy[47,48].

Knowledge Gaps: Given the similar macro- and microscopic features exhibited in both retained placentas as well as disorders of placentation such as preeclampsia, additional inquiry into the role of maternal vascular supply in the pathophysiology of retained placenta is needed.

Subinvolution of the Placental Site (Placental Bed Vascular Subinvolution, Subinvolution of Uteroplacental Arteries)

Definition: Failure of the uterine spiral arteries to return to the pre-gravid state[49].

Clinical Context: PPH due to subinvolution of the placental site most frequently occurs at 2 weeks postpartum[50], with reports of extensive bleeding as late as 6 weeks postpartum[51]. In a series examining tissue submitted from women with delayed PPH, subinvolution of the placental bed was the second most common finding, after retained products of conception[37]. Subinvolutional changes are also frequently seen in curettings that contain retained products of conception[37].

Proposed Pathogenesis: Early in gestation, the placental extravillous cytotrophoblast migrate to and invade the endothelium of the uterine spiral arteries in two stages, first involving the decidual vessels (6–10 weeks), with subsequent extension to the deeper myometrial vascular segments (14–15 weeks)[52]. This causes obliteration of the elastic and muscular medial tissue, which is replaced by fibrinoid material. Such remodeling physiologically transforms the normally high-resistance, low-capacity spiral arteries into distended uteroplacental arteries of low-resistance and high-conductance, a mechanism that ensures adequate blood supply to the fetoplacental unit[53].

Following delivery, the distended uteroplacental arteries involute, via thrombosis, regeneration of the elastic lamina, and loss of the trophoblast with consequent involution and contraction of the placental site [49]. This process happens within the first few days after delivery. The arteries are physiologically patent less than 24 hours after delivery, so subinvolution should not be diagnosed in this interval. Although the molecular mechanisms at work have yet to be entirely clarified, trophoblastic expression of the bcl-2 oncoprotein, associated with inhibition of apoptosis, has been demonstrated in normal involution of the placental site, with increased expression in cases of subinvolution. Interestingly, bcl-2 is not expressed in the uteroplacental vessels prior to delivery; leading to suggestion that subinvolution may represent prolonged survival of fetal trophoblast due to an exaggerated interaction with the colonized maternal tissues[54]. Without normal involution, implantation site vessels remain patent, allowing for increased bleeding. Sudden hemorrhage is thought to occur when partially occlusive thrombi are displaced.

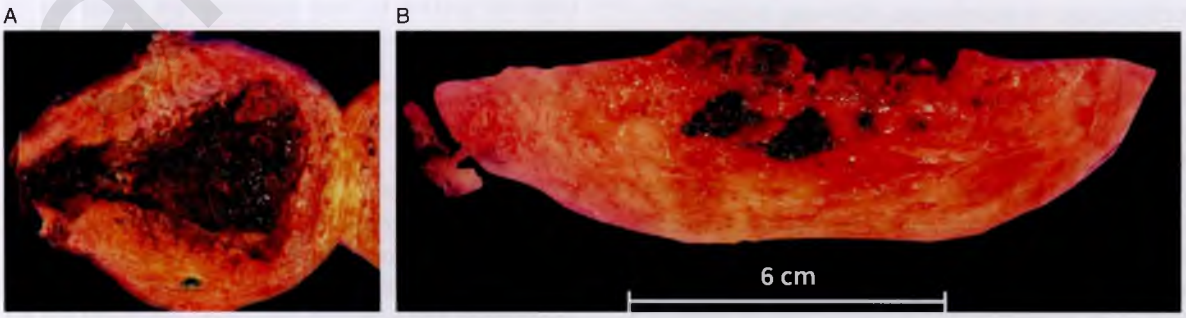

Figure 30.2 Postpartum hysterectomy from a patient with late PPH (10 days after low transverse cesarean section) secondary to subinvolution of the placental site. (a) The uterine cavity is filled with clotted blood. (b) Cross section of the uterine wall shows grossly dilated vessels in the upper half of the myometrium, which represent subinvoluted vascular spaces.

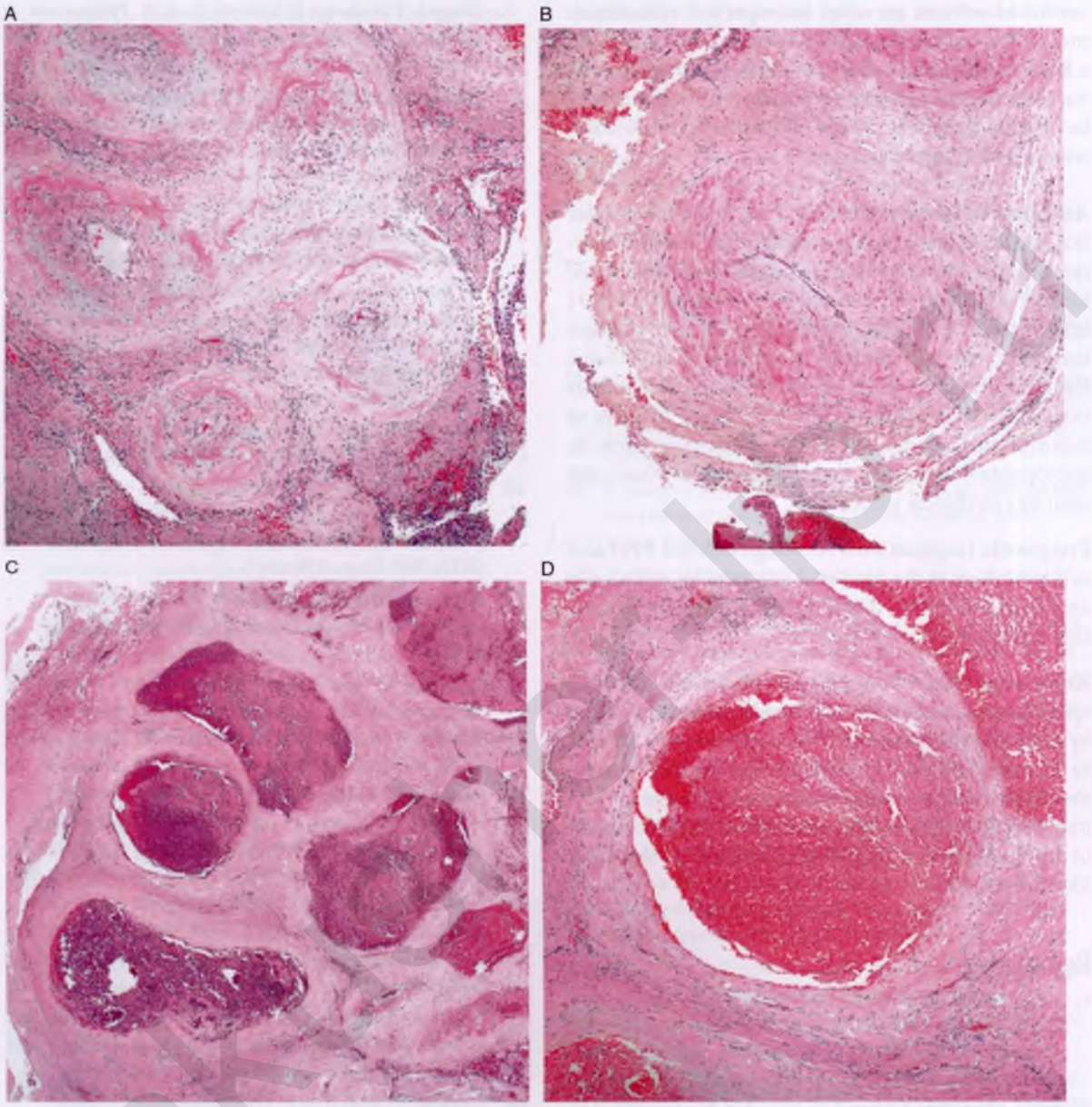

Figure 30.3 (a) Maternal arteries showing appropriate involution, with small lumina and fibroblastic proliferation. (b) Another vessel with appropriate involution showing smooth muscle proliferation and re-endothelialization. (c) and (d) Maternal arteries showing subinvolution characterized by widely patent, dilated vessels lacking fibroblastic proliferation, smooth muscle, or endothelial lining.

Gross Features: The uterus is increased in size, soft, and boggy. There may be ectatic, thrombosed arteries in the myometrial wall (Figure 30.2)[50].

Microscopic Features: Subinvoluted arteries are morphologically similar to those seen in the third trimester, exhibiting enlarged, dilated lumina with thickened and distorted walls and an absent endothelial lining (Figure 30.3c and d). The attenuated vascular walls are notable for deposition of eosinophilic hyaline matrix[55]. Patent vessels may be filled with red blood cells or partially organized thrombi[56]. Endovascular and interstitial extravillous trophoblast cells are identified on routine H&E staining as polygonal cells with abundant amphophilic cytoplasm and vesicular nuclei. Normally

involuted arteries are often interspersed with abnormal subinvoluted vessels. These are characterized by a fibroblastic proliferation which closes off or severely narrows the vascular lumen (Figure 30.3a). There may be re-endothelialization and regrowth of the muscular wall as well (Figure 30.3b).

Ancillary Diagnostic Testing: Peri- and endovascular trophoblast may be highlighted with the aid of immunohistochemical stains for low molecular weight cytokeratin. Although not necessary for diagnosis, a CD31 immunostain will highlight the endothelium of adjacent involuted vessels in contrast to the lack of endothelial lining in a noninvoluted vessel. Increased extravillous trophoblast expression of bcl2 is expected in cases of subinvolution, compared to weak staining seen in appropriately involuted vessels; however, we have not used this in clinical practice[54].

Prognostic Implications: Although delayed PPH and subinvolution of the placental site may be a clinically unrecognized entity, death due to uterine subinvolution has been reported[57].

Knowledge Gaps: As opposed to preeclampsia, where spiral arteries are thought to be inadequately remodeled by extravillous trophoblast[58,59], subinvolution appears to be associated with an excessive persistence of these elements. Further understanding of the cellular and immunologic basis of these interactions will be essential in developing future diagnostic and treatment strategies for both disorders.

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Chapter 31

Spontaneous Preterm Delivery (Premature Labor, Premature Rupture of Membranes, Vaginal Bleeding, Cervical Insufficiency)

Raymond W. Redline

Premature birth, delivery at less than 37 weeks gestational age (GA), is separated into two main groups: indicated preterm birth (IPB), where the delivery process is initiated for conditions not directly related to the onset of parturition (e.g. intrauterine fetal death, fetal growth restriction, maternal hypertension); and spontaneous preterm birth (SPB). SPB accounts for approximately 75 percent of all premature births and is further subdivided based on mode of initial presentation into four subgroups: preterm labor (PTL) accounting for 40 percent, preterm premature rupture of membranes (PPROM) 20 percent, vaginal bleeding (VB) 10 percent, and cervical insufficiency (CI) 5 percent[1–4]. While SPB ranging from 16 through 36 6/7 weeks GA represents a pathophysiologic continuum, the specific GA at delivery has profound and predictable implications for neonatal morbidity and mortality and also influences the relative frequency of underlying etiologies. The following GA subgroups have particular clinical relevance: previable (16–22 6/7 weeks), extremely low GA (23–27 6/7 weeks), very low GA (28–31 6/7 weeks), and late GA (32–36 6/7 weeks)[5,6].

Risk factors for SPB are often multiple and can be separated into three categories: maternal (chronic disease, obesity, stress, short stature, short interpregnancy interval, previous uterine instrumentation, smoking, very young age, black race, male fetus, bacterial vaginosis), fetal (male gender, growth restriction, multiple pregnancies, congenital anomalies), and placental as discussed below[6]. SPB has a high recurrence rate based on both persisting environmental risk factors and genetic predisposition[7]. Genetic studies indicate a complex multifactorial inheritance pattern with few strong individual candidate genes. Studies have shown that both maternal and fetal genotypes play significant roles[8,9]. Pathophysiological pathways under active study include myometrial contractility, cervical ripening, membrane activation, decidual senescence, hormonal stress responses, endothelial quiescence, complement and coagulation abnormalities, and immune response genes regulating reactivity to microbial virulence factors and fetoplacental alloantigens[10–12].

Previous studies have shown that placental findings in most premature deliveries fall into two categories, acute inflammation (chorioamnionitis) and maternal vascular malperfusion with little overlap[13,14]. SPB, as opposed to IPB, have a higher incidecn eof chorioamnionitis and tend to occur at an earlier gestational age. However, a significant proportion of SPB also show at least mild evidence of maternal vascular malperfusion (see below). Another important consideration is that early chorioamnionitis, particularly following PPROM, may represent secondary infection acquired after the initiation of parturition rather than its underlying cause. Other placental process that may contribute to SPB include maldevelopment (abnormal weight, shape, UC insertion site, dymorphic villi), old or recent hemorrhage (marginal or chronic abruptions), and alloreactivity (chronic chorioamnionitis or villitis/VUE). While it is generally acknowledged that the proportion of placentas with no detectable lesions in PTB increases with GA, there are few rigorous studies addressing whether absence of placental lesions is associated with a better neonatal prognosis. The clinicopathologic implications of each individual placental lesion for SPTB are discussed below.

Specific Lesions

Histologic chorioamnionitis (HCA) (see Chapter 12) developing as a result of primary ascending placental infections has been estimated to be the underlying cause of 25 percent of all preterm births[15]. The inflammatory response in HCA can be separated into maternal and fetal inflammatory components

each of which can be further subdivided according to intensity (grade) and duration (stage); see Chapter 12[16]. Prevalence of HCA in SPB varies from a high of 75 percent in the previable group to a low of 11 percent in the late group[17,18]. HCA is most frequent in the PPROM subgroup followed in order by CI, PTL, and VB[19–22]. Intensity, duration, and levels of circulating cytokines are all maximal at less than 28 weeks. Affected infants, especially those with a severe fetal inflammatory response at low GA, have alterations of fetal physiology including hypotension, abnormal myocardial contractility, and abnormal perfusion of the CNS[23–26]. It is believed that the combination of immaturity, circulatory derangements, and elevated cytokines synergize to elevate the risk of CNS injury (see Chapter 34) and, possibly, chronic lung disease[27–29]. No effects of HCA on umbilical artery pH have been noted and there is a generally protective effect against acute respiratory distress syndrome[30,31]. Infection is usually confined to the placenta, but an increased risk of neonatal sepsis has been observed with HCA and placental examination may identify infants requiring extended antibiotic therapy[32]. Distinct histology also helps identify clinically important subgroups caused by fungi and *Listeria monocytogenes*[33,34]. Cases of SPB with HCA have an elevated recurrence risk compared to those without and the recurrences are also significantly more likely to show HCA[35].

Acute marginal abruption (see Chapter 11) presenting as acute VB in SPB is most commonly caused by marginal venous rupture[36]. Placental evidence of marginal abruption (disc indenting clots and microscopic hemorrhage) is seen in 40 percent of SPB compared to less than <10 percent at term[37,38]. VB can accompany other placental lesions, particularly HCA at early GA, but marginal abruption is the sole pathologic finding in approximately 5–10 percent of cases of SPB. Marginal abruptions are both potential causes (via thrombin activated membrane weakening) and frequent sequela (due to altered marginal support after loss of amniotic fluid) of PPROM[3]. Underlying risk factors for marginal abruption include older maternal age, multiparity, and smoking. Aside from playing a causative role in premature delivery, no specific maternal or neonatal adverse outcomes have been associated with acute marginal abruption.

Chronic abruption (see Chapter 11) is caused by recurrent marginal venous hemorrhages occurring remote from birth and is a strong risk factor for SPB[39]. These hemorrhages are often associated with a clinical history of first or second trimester bleeding and may be accompanied by a "subchorionic hematoma" on early ultrasound[40,41]. Early subchorionic hematomas are found in 0.5–22 percent of all screened pregnancies and are also risk factors for miscarriage and stillbirth. In addition to VB, they may also contribute to later CI or PPROM. Maternal risk factors for chronic abruption overlap with those listed above for marginal abruption. Associated histologic placental lesions include circumvallate membrane insertion, organizing marginal blood clots, and chorioamnionic hemosiderosis[42–45]. Preterm neonates with diffuse chorioamnionic hemosiderosis are at increased risk for an atypical form of chronic lung disease[44,45].

Maternal vascular malperfusion (MVM) (see Chapter 7) is most common with IPB, especially those cases preceded by maternal preeclampsia or FGR with abnormal Doppler studies[46]. However, as mentioned above, many authors have reported a relatively high prevalence of MVM in all four subgroups of SPB (PTL, PPROM, VB, CI), especially after 28 weeks[17,47–49]. Notably, decidual arteriopathy on placental bed biopsies is increased with both PTL and PPROM and accelerated villous maturation has been found in over a third of cases of PTL and PPROM[50]. Etiologic factors common to both MVM and SPB include maternal obesity, underlying maternal lipid abnormalities, and occult maternal autoantibodies. The pathogenesis of SPB associated with MVM may include membrane ischemia (histologic laminar necrosis) and the release of mediators such as fetal cell free DNA, which can activate maternal inflammatory responses and the labor cascade[10,51].

Idiopathic chronic inflammatory lesions (see Chapters 13 and 14) associated with maternal adaptive immunity, including *lymphoplasmacytic deciduitis* (B cells) and *chronic chorioamnionitis* (T cells) have recently emerged as distinct potential causes of SPB. Lymphoplasmacytic deciduitis is a common, but nonspecific, inflammatory lesion that can accompany either chronic villitis or acute chorioamnionitis[52]. However, it is also commonly found alone and is more frequent in SPB than either IPB or term birth[53]. Whether it reflects a response to bacterial antigens, autoantigens, or alloantigens within the maternal endometrium is not settled. A very recent study suggests that

B cells play a specific role in preventing preterm labor and that dysfunctional B cells accumulate in the decidua of placentas from sPTB[54]. Chronic chorioamnionitis is defined by patchy-diffuse infiltrates of T cells in the chorion and amnion of the placental membranes (see Chapter 14). The lesion shares a common T cell chemokine signature with chronic villitis/VUE and it has been suggested that it may represent a graft versus host type reaction to fetal stromal cells in the amnion and chorion[55]. Several recent studies from the Romero group have found this lesion to be a major contributor to SPB, particularly in later GA subgroups[17]. However, the lesion is subtle, diagnostic criteria are nonspecific, prevalence varies widely (between 9–26 percent for late SPB), and further study is necessary.

Finally, underlying developmental abnormalities confined to the placenta (abnormal measurements, abnormal shape, nonparacentral UC insertion site, and dysmorphic villi) are often seen in cases of SPB lacking other fetal or placental pathology. These potential risk factors for SPB are understudied, and the reader is referred to Chapters 9 and 16 for further discussion of this heterogeneous group of lesions.

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Chapter 32

Fetal Growth Restriction

Ann Folkins

Fetal Growth Restriction (Intrauterine Growth Restriction, Small for Gestational Age)

Definition: Small for gestational age (SGA) refers to fetal birth weight <tenth percentile for gestational age. Fetal or intrauterine growth restriction (IUGR), refers to fetuses with an estimated fetal weight below the tenth percentile[1]. Prenatal ultrasound is used to estimate fetal weight. SGA infants likely represent two groups: constitutively small infants who are otherwise healthy and pathologically growth restricted infants. The use of a tenth percentile cut off for the definition of SGA/IUGR is imperfect but is currently the standard method to identify infants/fetuses who may be growth restricted. Growth restriction has been classically divided into symmetric and asymmetric categories[2,3]. Symmetric growth restriction refers to a relatively equal reduction in body weight and head circumference. This occurs in the setting of conditions impairing cell division early in pregnancy which reduce growth potential, such as an infection, congenital malformation, or chromosomal abnormality. Infants with symmetric growth restriction usually follow the same growth curve percentile during the pregnancy. Asymmetric growth restriction refers to a reduction in the body weight with a relatively normal head circumference. This occurs in the setting of disorders affecting nutrient and oxygen delivery to the fetus in mid to late pregnancy. Blood is preferentially redirected to the brain by the growing infant. These infants may fall off their previous growth curve during serial ultrasounds. In practice, there is significant overlap in growth restriction patterns over time. It is also important to note that some symmetrically growth restricted fetuses who grow normally over the pregnancy may represent constitutionally small infants.

Clinical Context: In the United States, the overall rate of SGA births is approximately 10 percent according to the Centers for Disease Control and Prevention (CDC)[4]. The prevalence of SGA birthweight varies geographically and also by whether it is term or preterm. The rate of term SGA births has been decreasing in the United States, while the rate of preterm SGA births has been increasing. From 1975 to 2000, term SGA births in the United States decreased from 21 percent to 16 percent among blacks and from 12 percent to 9 percent among whites[5]. Preterm birth rates have been increasing in the past several decades in high income countries, and there is a parallel increase in preterm SGA rates[6]. In low and middle income countries, the prevalence of term SGA infants ranges from 5.3 percent to 41.5 percent and preterm SGA infants range from 1.2 percent to 3 percent. The highest rates of SGA infants are found in Southeast Asia[7]. Detection and monitoring of fetal growth restriction is challenging; ultrasound evaluation is currently the best method available. Fundal height measurements (24–38 weeks) are used to screen for IUGR during routine prenatal visits; however, physical exam alone detects only a small proportion of cases in low risk populations[8]. Ultrasound uses biometric measurements such as bipareital diameter, head circumference, abdominal circumference, and femur length to calculate the estimated fetal weight. When IUGR is detected during a pregnancy, follow-up ultrasound examinations are performed to assess amniotic fluid volume and biometry. This should include measurement of umbilical artery flow by Doppler velocimetry, as this has been shown to significantly reduce mortality[1,8]. Absent or reversed end-diastolic umbilical artery flow carries an increased risk of perinatal mortality and is usually an indication for delivery of the fetus. Umbilical artery flow measurement alone does not detect mild placental dysfunction, which is often present in cases of late onset growth restriction[9]. Therefore, other measurements, such as middle cerebral artery and uterine artery flow Doppler, are also now used to monitor growth restricted fetuses[8]. The cerebroplacental

Table 32.1 Factors associated with fetal growth restriction

Fetal	Placental	Maternal
Chromosomal abnormalities	Maternal vascular malperfusion	Pregnancy-related hypertensive disorders
Congenital malformations	Chronic villitis	Anti-phospholipid antibody syndrome
Congenital infection	Chronic abruption	Diabetes mellitus
	Fetal vascular malperfusion	Autoimmune disorders
	Maternal floor infarction/ massive perivillous fibrin deposition	Heart disease
	Confined placental mosaicism	Renal disorders
	Placental mesenchymal dysplasia	Malnutrition
	Twin-twin transfusion	Smoking
		Substance abuse
		Teratogen exposure

ratio (CPR) combines the pulsatility index of the middle cerebral artery and the umbilical artery and may better predict adverse outcomes in growth restricted fetuses[10].

Proposed Pathogenesis: Factors contributing to IUGR can be generally regarded as fetal, maternal, or placental (Table 32.1)[1]. Fetal factors include genetic abnormalities, structural malformations, and congenital infections, such as cytomegalovirus or malaria. Growth restriction due to fetal factors involves an intrinsic reduction in the growth capacity of the fetus, while growth restriction due to maternal and placental factors usually involves impaired nutrient and oxygen delivery to the fetus. Maternal conditions include pregnancy-related hypertensive disorders, antiphospholipid antibody syndrome, diabetes mellitus, autoimmune disease, heart disease, and renal disorders. Smoking, substance use/abuse, and teratogen exposure are also associated with an increased risk of growth restriction. Any significant compromise of the placental capacity to exchange nutrients and oxygen can lead to IUGR. Conditions which can impair the placental function include uteroplacental malperfusion (often secondary to underlying maternal vascular disease), fetal vascular malperfusion, high grade chronic villitis of unknown etiology (VUE), chronic abruption, and maternal floor infarction (MFI)/massive perivillous fibrin deposition (MPFD)[11]. Confined placental mosaicism and placental mesenchymal dysplasia have also been linked to fetal growth restriction[12,13]. Fetuses from multigestation pregnancies are often growth restricted, most commonly the fetus with a smaller placental territory. Of course, twin-twin transfusion syndrome results in growth restriction of the donor fetus.

Gross Features: Placentas from fetuses that are growth restricted due to a placental etiology are usually small for gestational age (<tenth percentile). The presence of pathologic features of maternal vascular malperfusion really depends on the severity of the growth restriction and the gestational age of onset. If it is a premature infant with severe growth restriction (<third percentile), there may be placental infarcts, a narrow umbilical cord (<0.8 cm average diameter at term), retroplacental hematoma, or a thin disc. These features are less often noted in term growth restricted infants presumably because the process is not as severe. Overall, if growth restriction is related to a placental etiology, early onset cases are typically associated with more severe placental pathology and late onset cases may have only subtle pathologic features[14]. Cord abnormalities, including true knots, hypercoiling or marginal/velamentous insertion may be present in cases of fetal vascular malperfusion. Diffuse villitis can result in white mottling of the parenchyma. If there is chronic abruption, there may be circumvallate membrane insertion, brown discoloration, and marginal adherent organized blood. An orange-rind-like layer of fibrin at the maternal surface or diffuse marbling of the parenchyma by fibrin should raise suspicion for MFI/MPFD.

Microscopic Features: The microscopic features associated with IUGR depend on the underlying etiology; these are best explained in the individual chapters for these disorders. Brief summaries of the most common disorders are provided here. Maternal vascular malperfusion can result in ischemic changes within the terminal villi, namely accelerated villous maturation or distal villous hypoplasia (Chapters 5–7). There may be multiple infarctions and decidual vascular arteriopathy may be present in scattered maternal spiral arteries. Fetal vascular malperfusion may be identifiable by foci of avascular villi or villous stromal karyorrhexis with or without fetal vascular thrombi (Chapter 10). Chronic villitis will manifest as a lymphocytic infiltrate primarily within the villi (Chapter 13). In chronic abruption, there will be numerous hemosiderin-laden macrophages in the membranes and abundant organized hemorrhage (Chapter 8). MFI/MPFD will be associated with a significant increase in perivillous or basal plate fibrin(oid) material (Chapter 17).

Ancillary Diagnostic Testing: There are no routine ancillary diagnostic tests to perform on placentas from growth restricted infants. Tests may be performed as directed based on the clinical and pathological findings (e.g. CMV immunohistochemistry if plasma cell chronic villitis is present).

Prognostic Implications: Growth restricted infants are at increased risk for neonatal morbidity and mortality [15][3]. Neonatal morbidities include hypoxia, hypoglycemia, hypothermia, hyperbilirubinemia, and polycythemia. Infants born premature are also at risk for complications related to prematurity, such as intraventricular hemorrhage and necrotizing enterocolitis[16,17]. Long-term sequelae include increased risk of cardiovascular disease[18]. Currently, there is no therapy to improve fetal growth; the primary intervention is delivery of the fetus before intrauterine demise or organ damage. Unfortunately, the detection rate of IUGR is low, so many cases go unnoticed, resulting in an increased risk of stillbirth[19]. Early onset fetal growth restriction can often by detected by first and second trimester screening ultrasounds, but late onset cases are often missed[8]. Notably, a low fetoplacental weight ratio (FPR) may be useful in distinguishing pathologically growth restricted infants from constitutional small infants in the SGA group[20]. Identification of placental causes for growth restriction is important, as many of these conditions can recur in subsequent pregnancies. Therefore, there is an opportunity for prevention of future pregnancies with growth restriction or at least serial monitoring to assess growth.

Knowledge Gaps: Accurate and timely detection of IUGR still remains challenging. Maternal blood biomarkers, such as soluble fms-like tyrosine kinase-1 (sFlt-1) may be useful in the future as an adjunct to ultrasound[8]. Delivery of the fetus is the only "treatment" for IUGR at this time. However, there is research into therapies for poor placentation (maternal vascular malperfusion), which may help to improve fetal growth once growth restriction is detected prenatally[21,22].

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Chapter

33 Fetal Death

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Definition: Fetal death (stillbirth, intrauterine fetal demise) refers to the cessation of intrauterine life prior to delivery. This terminology is by convention usually restricted to the latter half of gestation, and more specifically to the period of gestational viability (24+ weeks until term).

The gestational mechanisms that result in fetal death share many overlapping characteristics with the causes of other untoward outcomes covered in this section (Chapters 31–35). As a general principle, intrauterine disorders associated with deleterious fetal and neonatal effects tend to be advanced/extensive, relative to the spectrum that can be seen with any given disorder. This is particularly true of subacute and chronic placental processes. In fact, fetal death can be viewed as the ultimate injury of intrauterine origin. This chapter covers the most common intrauterine disorders associated with stillbirth following gestational viability. With the exception of certain catastrophic events, each of these processes creates tell-tale placental findings ("footprints").

Individual pathologic mechanisms can generally be clustered into pathophysiologic modes, or common pathways. The modes covered herein include intrauterine infection, hypoxia, and maternal immune dysregulation. Other modes associated with intrauterine demise, such maternal metabolic disorders (e.g., hypo- and hyperthyroidism), and intrinsic fetal disorders (e.g., aneuploidies in later gestation) will not be addressed, as they generally bear no specific placental footprints.

The following disorders are clustered into categories based upon the general span of time over which they occur prior to demise. The list is not meant to be exhaustive, but rather to focus on mechanisms that are 1) operative following gestational viability, and 2) relatively commonplace, or less common but distinctive. This chapter is limited to placental features specifically relevant to fetal death. Other disorders that manifest in placental pathology are covered in detail elsewhere in this text.

Of note, there may be synergistic effects when multiple pathologic processes are present, with each contributing to lowered fetal threshold for tolerating additional *in utero* pathologies. The pathways may be inter-related with respect to underlying cause, or may by happenstance occur simultaneously.

As examples of the former (primary cause leading to multiple pathways):

1) Fetuses of diabetic mothers are predisposed to fetal vascular malperfusion through a number of pathways related to fetal hyperglycemia (see Chapter 10). Placentas may concomitantly exhibit placentomegaly with delayed villous maturation (see Chapter 9), which, independent of the effects of hyperglycemia, are risk factors for untoward neonatal outcome.
2) Growth-restricted fetuses of pre-eclamptic mothers often have growth restricted placentas exhibiting features of maternal vascular malperfusion (see Chapter 7). These placentas are also prone to fetal vascular malperfusion by mechanisms related to aberrant placental growth, such as narrow umbilical cord and abnormal cord insertion, as well as an increased risk of cord compression due to oligohydramnios (see Chapters 10 and 16).

As an example of coincident independent pathologic processes associated with untoward outcome, advanced amniotic fluid infection may be present in a pregnancy complicated by high grade non-infectious chronic villitis.

Thus, multiple placental effects that are related to a single cause or independent causes can operate additively or synergistically to culminate in fetal death.

Catastrophic ("Sentinel") Events (Minutes to Hour[s])

Catastrophic events, clinically recognized as obstetric emergencies, lead to rapid escalation of fetal hypoxia.

The following entities are those that fundamentally involve the placenta.

Traumatic acute placental abruption (see Chapter 8) occurs in unexpected circumstances that impart external mechanical forces to the maternal abdomen, leading to forceful separation of the placenta from the uterine wall. The hallmark feature of traumatic abruption is the observation of placental separation with extensive intrauterine blood at the time of delivery. Fetuses who sustain an instantaneous reduction in placental oxygenation tolerate its extent much more poorly than those who sustain the same or an even greater extent of reduction in placental oxygenation that accumulates over time. It has been estimated that rapid onset acute placental abruption involving >45 percent of the placental disc is sufficient to lead to rapid fetal death[1].

Umbilical cord prolapse refers to the umbilical cord dropping into the vaginal canal prior to the presenting fetal part during the intrapartum. This medical emergency typically occurs in preterm fetuses, where there is sufficient intrauterine space due to smaller fetal size for the umbilical cord to exit between the fetus and the uterovaginal wall. Upon recognition, the fetal presenting part is manually supported by introduction of a practitioner's hand into the vaginal canal. Thereafter, if the umbilical cord is not reducible back into the uterine cavity, emergency Cesarean section is indicated. Until the fetus is delivered, it is imperative that the fetal presenting part continues to be elevated to prevent fetal death[2]. There are no hallmark gross or microscopic placental or umbilical cord features; thus, the diagnosis is a clinical one.

Ruptured vasa previa (see Chapters 11 and 16) refers to extrachorial extension of chorionic vessels, traversing the endocervical os within the extraplacental membranes. Spontaneous membrane rupture in either unrecognized vasa previa or prior to planned Cesarean section leads to transection of extrachorial vessels at the membrane rupture site. Vasa previa almost always occurs in placentas that are low lying. These low lying placentas are often initially identified by prenatal ultrasound as placenta previas, that then tend to resolve as pregnancy proceeds and placental disc growth polarizes toward the uterine fundus. Umbilical cord insertion is almost always marginal or velamentous. Mothers present with vaginal bleeding, but without signs/symptoms characteristic of placental abruption. Fetal monitoring reveals either fetal demise or significant fetal distress. The infant mortality rate for vasa previa is approximately 20-fold greater than in pregnancies without vasa previa[3], due primarily to the risk of rapid fetal exsanguination following rupture. Mortality rates increase with increasing gestational age > 37 weeks; thus, scheduled preterm delivery is typically indicated[4].

Acute Events (Hours to ~ a Day)

Atraumatic acute placental abruption, +/- uterine rupture (see Chapters 8 and 29, respectively) occurs in the clinical context of predisposing maternal conditions, including all manner of hypertensive disorders, such as chronic hypertension, preeclampsia, and HELLP. Certain maternal autoimmune disorders – the lupus anticoagulant family of autoantibodies, connective tissue disorders, and pregestational insulin dependent diabetes mellitus with superimposed vascular disease – are also associated with placental abruption. Uterine rupture, in the context of placental abruption, occurs in circumstances of prior uterine wall instrumentation, such as Cesarean section or D&C (dilatation and curettage); or with circumstances leading to intrapartum uterine hypertonicity such as excessive pitocin administration[5]. Atraumatic placental abruption can occur as a result of hypertension, with pathologically high spiral arteriolar pressures, or with intrinsic pathologic vascular changes (e.g., severe decidual arteriopathy) that predispose to vessel rupture. Uterine rupture often occurs when placental implantation involves the prior instrumentation site. In circumstances of placental abruption that lead to fetal/neonatal demise, with or without uterine rupture, the clinical findings are usually dramatic. Relevant maternal signs and symptoms include: severe abdominal pain, uterine tetany, pronounced vaginal bleeding, retroplacental blood accumulation on ultrasound, bloody amniotic fluid, spontaneous placental detachment, and intrauterine blood clots at the time of delivery. Fetal signs include severe fetal distress or absent fetal heart rate, meconium discharge, suction of bloody neonatal oropharyngeal fluid, intra-abdominal fetal presentation at Cesarean delivery, and neonatal pallor if fetal hemorrhage occurs as a consequence of placental tearing. Atraumatic placental abruption with fetal demise is associated with an increased risk of recurrent fetal morbidity and mortality in maternal disorders that are either unmodifiable or cannot be safely modified in the context of pregnancy. Uterine rupture

can recur if hysterectomy is not performed in the index pregnancy.

Spontaneous umbilical cord rupture (see Chapter 16), a rare event (1 in 5,000–11,000 deliveries)[6], is first recognized as the sudden onset of intrapartum fetal distress that does not resolve with resuscitative efforts, necessitating emergent delivery. The etiology of spontaneous cord rupture, in most circumstances, is unknown. Occasionally, pathologic examination may show mural changes that explain the umbilical vessel weakening. Affected umbilical cords often demonstrate an engorged region that measures several centimeters in length, with diameters that are multiple times that of normal cords. The overall effect is of a plethoric sausage-shaped umbilical cord lesion. Hemorrhage extends broadly into Wharton's jelly, causing marked distension, and extends microscopically for several centimeters of sampled cord in either direction of the rupture site. Although clinical fetal distress appears suddenly, there are often microscopic features that indicate some degree of perivascular bleeding having occurred in a non-acute time frame preceding complete rupture. Fetal death can be due primarily to vascular compression secondary to hemorrhagic "tamponade" within Wharton's jelly; consequent fetal anemia likely plays a minor role. The mortality rate is an estimated 50 percent[6]; neonatal survival is associated with neonatal asphyxia and neurologic deficits[7].

Sub-Acute Events (Days)

Amniotic fluid infection (see Chapter 12), though common, uncommonly results in fetal demise following gestational viability. This is usually due to the fact that intra-amniotic fluid infection stimulates labor, eventuating in delivery before fatally deleterious effects occur. As time progresses between the onset of infection and delivery, risk factors for demise increase. These include: delivery at a pre-viable stage of gestation; direct placental effects of inflammation, particularly intense fetal inflammation leading to altered vascular tone, with or without thrombosis; systemic fetal effects of intrauterine inflammation via cytokines and other mediators; and the development of fetal infection as pneumonia and/or sepsis. Modifying factors include bacterial virulence, antenatal antibiotic administration, gestational age, and concomitant intrauterine processes that elevate the risk of untoward fetal/neonatal outcome[8].

Fetal vascular malperfusion (see Chapter 10) represents non-acute fetal blood flow restriction, typically due to mechanical causes of umbilical blood flow compromise. Fetal malperfusion as a cause of intrauterine demise is most common at term, though fetal demise also occurs earlier in the third trimester, and rarely during the second trimester. Clinically, evolving malperfusion is generally silent. The most typical presentation is maternal recognition of decreased fetal movement in the day(s) prior to seeking medical attention. Both patterns of fetal malperfusion, segmental (total) and global (partial), are not only causative of demise but are also associated with evidence of antemortem histologic neuronal injury in the stillborn fetus, suggesting an etiologic – though perhaps not directly causative – risk of neurodiability among livebirths (see Chapter 34). The segmental (total) pattern exhibits thrombi in muscular intraplacental fetal vessels and large foci of avascular villi, presumably due to thrombotic occlusion of chorionic and/or stem villous vessels. The global/partial pattern, attributed to persistent or recurrent but incomplete cord obstruction, is characterized by venous ectasia, intramural fibrin in chorionic or stem villi, and small foci of avascular villi. Histologic criteria for fetal vascular malperfusion that incorporate both patterns as causative of stillbirth have been published[9,10].

Fetal maternal hemorrhage (see Chapter 11) occurs via fetal bleeding into the maternal intervillous circulation of the placenta. Fetal maternal hemorrhage (FMH) may be the direct consequence of mechanical abdominal trauma, such as with motor vehicle accidents, forward falls, or a secondary consequence of placental abruption, but in the majority of cases (~80 percent) FMH is clinically silent, without a known inciting event[11]. In one study, fetal death was the presenting sign in 12.5 percent of all cases of confirmed FMH[12]. Fatal FMH is usually considered acute (as opposed to chronic FMH), though microscopic evidence of normoblastemia indicates hemorrhage occurs over hours to day(s) prior to demise (see Chapter 20). Placentas are pale, and fetal vessels variably hypo- to avolemic, but rarely is the locus of intraplacental hemorrhage identified grossly. Exceptionally, there is a fresh intervillous thrombus that contains fetal blood as evidenced by intervillous nucleated red blood cells or positive immunostaining for fetal hemoglobin.

Chronic Events (Weeks)

Noninfectious chronic villitis/ VUE (see Chapter 13) is believed to represent a maternally derived host versus graft response to unknown fetal/placental/ intrauterine antigens. Immunophenotypically, the maternal infiltrate is comprised of T lymphocytes with a variable secondary component of inflammatory monocyte-macrophages. Chronic villitis of noninfectious etiology leads to untoward fetal/neonatal outcome, including intrauterine growth restriction, neurodisability in live births, and stillbirth, when it is extensive, otherwise designated as high grade[10,13,14]. Proposed pathogenic mechanisms include direct inflammatory damage as well as secondary ischemic effects (avascular villi) owing to involvement of stem vessels (stem vessel obliteration). Conceptually, there could also be fetal somatic vasoactive effects, most notably within the cerebral vasculature.

Chronic histiocytic intervillositis (see Chapter 15) (CHI) is also believed to represent an aberrant maternal immune response to unknown fetal/placental/ environmental antigens. There are no hallmark gross features, but histologically there is infiltration of the intervillous space by maternally derived phenotypically mature histiocytes, admixed with fibrin. CHI is rare, but when identified is associated with a high risk of recurrent pregnancy loss, particularly in the first trimester, due perhaps to intervillous fibrin interference with maternal-to-fetal oxygen and nutrient delivery. With pregnancies that survive to viability, CHI is associated with intrauterine growth restriction and, uncommonly, with stillbirth[15]. The mechanism of untoward outcome at this stage is less apparent, as the microscopic pathology reveals fewer intervillous histiocytes and less substantial fibrin accumulation. Nevertheless, in affected later gestations, the recurrence risk remains high. To date, preventive therapy with immunomodulatory agents remains empiric and variably effective.

Maternal floor infarction/ massive perivillous fibrin deposition (see Chapter 17) is associated with fetal death and a high risk of recurrence in future pregnancies. This pattern of injury has been associated with fetal LCHAD mutations, maternal vascular malperfusion, and Coxsackie virus infection, but most cases are considered idiopathic. There is, however, mounting evidence that the etiology involves maternal immunologic dysregulation to fetal/placental antigens, e.g., maternally derived anti-fetal HLA antibodies[16]. As with other mechanisms of chronic intrauterine stress, the evolution is typically silent. Recognition of this disorder occurs only with placental examination after delivery. Pathophysiologically, placental "dysfunction" leading to fetal demise is attributed to progressive entrapment of functional villous parenchyma by perivillous fibrin[17].

Maternal vascular malperfusion (see Chapter 7) is a less common isolated cause of fetal demise in developed countries, since routine antenatal surveillance identifies at-risk fetuses. Indicated preterm delivery is effected if medical intervention is inadequate to prevent clinical signs portending fetal deterioration. These include interval lags in fetal growth, diminished biophysical profile, and ultrasound evidence of placental dysfunction. Prenatal fetal, umbilical and uterine artery Doppler flow studies have been shown to be of specific predictive value for risk of stillbirth[18,19]. In under-resourced countries, however, maternal malperfusion remains a primary cause of intrauterine demise. Underlying maternal disorders are broadly subclassified into those mediated by hypertension and those mediated by the effects of maternal autoimmunity.

Placental hydrops (see Chapter 11) is always secondary to another underlying pathophysiologic process. The causes are manifold, and can be of intrinsic fetal origin (e.g., cardiac malformation such as Ebstein's anomaly, sacrococcygeal teratoma), maternal origin (e.g., alloimmune fetal hemolysis such as Rh incompatibility), placental origin (e.g., chronic fetal maternal hemorrhage), or exogenous origin (e.g. parvovirus B19 infection). Intrauterine demise occurs if hydrops is undetected or if medical interventions are ineffective, though with close surveillance and management survival occurs in ~90 percent of affected fetuses[20]. The risk of recurrence is negligible if intrinsic underlying causes such as maternal alloimmunity can be controlled. Unavoidable recurrent affected pregnancies (e.g., Hb Bart's alpha thalassemia) are usually terminated.

Diabetes-associated fetal death (see references in Chapters 9 and 10) occurs through a number of pathophysiologic mechanisms that are related to the effects of maternal hyperglycemia. In the fetus, maternal hyperglycemia leads to fetal hyperglycemia, which in turn can lead to hypercoagulability. This is mediated in part by hyperosmolarity due to excess blood glucose, and in part by glucose stimulation of

erythropoietin, resulting in polycythemia. In the fetus, somatic (e.g., renal vein) thrombosis can result, as it also can in the placental fetal circulation, leading to fatal fetal vascular malperfusion. The fetus is also at risk for hypertrophic cardiomyopathy, a direct cause of fetal death. Fetal hyperinsulinemia can result in diabetic placentomegaly, chorangiosis, and delayed villous maturation; the latter of which has been associated with intrauterine demise, possibly by reducing the placental reserve to withstand subsequent, perhaps even minor, stressors in late pregnancy. Maintenance of maternal glycemic control is the single best predictor of pregnancy outcome[21].

Mesenchymal dysplasia and other occult villous dysmorphologies (see Chapter 9) associated with karyotypically normal fetuses share in common confined placental mosaicism. Mechanisms that lead to intrauterine demise in dysmorphic placentas include generalized lack of adequate placental function to maintain normal fetal growth; intrinsic cellular defects (e.g., metabolic) associated with specific mutations, and compartment-specific abnormalities such as fetal vascular malperfusion in mesenchymal dysplasia, or maternal vascular malperfusion in confined placental mosaicism for trisomy 16. In addition, submicroscopic placental dysfunction due to genetic/chromosomal aberrations may not always have observable pathologic correlates. The risk of stillbirth with mesenchymal dysplasia has been reported at 30 percent[22].

Giant chorangioma, extensive multifocal chorangiomatosis, and multiple chorangioma syndrome (see Chapter 9) can cause fetal death via excess capillary beds that function as a vascular reservoir. The resulting "steal" of fetal blood volume from the normal placental-fetal circulation leads to a combination of cardiac failure, hydrops and lethal fetal hypoxia. The etiology is unknown, though not surprisingly, enhanced expression of angiogenic growth factors (e.g., angiopoietin) has been demonstrated[23].

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Chapter

34 Central Nervous System Injury

Raymond W. Redline

One of the major purposes of placental examination is to understand adverse pregnancy outcomes. Perhaps no outcome is more devastating to both parents and caregivers than central nervous system (CNS) injury, leading to lifelong functional impairments that prevent a child from reaching his or her full potential. Amongst the perinatal processes associated with CNS injury are neonatal encephalopathy, intraventricular hemorrhage, periventricular hemorrhagic infarction, gray matter/neuronal injury, white matter/oligodendroglial injury, and arterial and venous perinatal stroke. Long-term adverse outcomes related to these processes include cerebral palsy and related motor disorders, seizure disorders, microcephaly, and cognitive impairment.

Understanding the etiology of fetal CNS injury requires careful consideration of family history, clinical risk factors, antenatal testing, peripartum events, evolving neonatal status, and placental pathology. Given what we know about the pathophysiology of CNS injury, failure to take advantage of the rich and varied information provided by placental examination is a mistake that family members and physicians will likely regret. Beyond gaining insights into causation, more recent work suggests that some placental lesions, such as chronic villitis, may predict lack of response to head cooling in infants with neonatal encephalopathy[1]. Clarification of differing mechanisms of injury associated with specific placental lesions may facilitate the development of targeted therapies in the future.

Before considering the specific placental processes most closely associated with fetal CNS injury, it is instructive to review potential mechanisms of injury. Perinatal stressors can be separated into vascular and inflammatory subgroups with the realization that combinations of these stressors may be most significant (see "Multiple Placental Lesions," below). Premature infants represent a somewhat distinct group in that they enter parturition before completion of CNS development. The absence of placental trophic factors that are available to infants who remain in utero can compromise the capacity of those born early to resist damage and repair injury[2,3]. This pathway to injury has called "paucity of protection." Premature fetuses also have greater cardiovascular instability, lack autoregulation of cerebral blood flow, and tend to have higher levels of inflammatory cytokines; all features which predispose to CNS hemorrhage, impaired oligodendroglial maturation, and white matter damage[4].

Placental vascular processes contribute to CNS injury in several ways[5]. Sudden severe hypoxia (total asphyxia) occurs when placental vascular events separate the fetus from its maternal oxygen supply. These so-called sentinel events, including profound maternal hypotension, placental abruption, and UC occlusion directly cause ischemic brain injury. Most common in term infants, they progress through a sequence of so-called birth asphyxia, neonatal encephalopathy, and either death or cerebral palsy of the spastic quadriplegic type with additional developmental disabilities[6,7]. Lesser degrees of ischemia in the peripartum period can also cause CNS injury, particularly in the face of previous sensitization (e.g. by repetitive episodes of intermittent hypoxia, activation of the coagulation cascade, or fetoplacental inflammation)[8]. This scenario is sometimes called "partial prolonged asphyxia." Other important concepts include decreased placental reserve due to parenchymal disease which can decrease the capacity to withstand acute hypoxia and chronic ischemic preconditioning which increase this capacity[9,10].

Relevant placental inflammatory processes fall into three groups. (1) Acute chorioamnionitis, bacterial infection of the placenta, exposes the fetus to proinflammatory bacterial molecules (so-called PAMPs) and innate inflammatory mediators including chemokines and cytokines. These mediators are concentrate in the amniotic fluid and can either be aspirated or released into the fetal circulation by fetal inflammatory cells[11]. (2) Chronic villitis/VUE,

a maternal T-cell mediated allograft response to fetal antigens in the villous stroma, is also associated with elevated fetal chemokines and cytokines. In this case, the inflammatory mediators are those associated with adaptive immunity[12]. (3) Finally, recent studies suggest that certain metabolic conditions, such as maternal obesity, cause "noncellular" inflammation that may activate placental cells to secrete inflammatory mediators into the fetal circulation[13,14]. Histologic correlates of the last process have yet to be described.

Specific Placental Lesions

Histologic acute chorioamnionitis (see Chapter 12) has been associated with a diverse group of CNS disorders including white matter damage, intraventricular hemorrhage, retinopathy of prematurity, neonatal encephalopathy, cerebral palsy, stroke, seizures, developmental delay, and neuropsychiatric diseases[1,15–22]. Evidence specifically implicates the fetal inflammatory response in chorioamnionitis, particularly umbilical arteritis (associated with elevated levels of IL-6 in the neonatal circulation) and high grade histologic inflammation in chorionic plate vessels (defined by near confluent neutrophilic infiltrate with endothelial activation/damage and in some cases recent mural thrombi)[23,24]. High grade histologic fetal inflammatory responses have been associated with cerebral palsy in preterm and term infants and neurocognitive deficits at school age[25–27].

One caveat to the widely acknowledged association of chorioamnionitis with CNS injury is that for preterm infants it may be difficult to disentangle the confounding effects of gestational age and maternal vascular malperfusion. Specifically, most cases with chorioamnionitis are delivered earlier without maternal vascular malperfusion while most cases without chorioamnionitis are delivered later and show evidence of maternal vascular malperfusion, both of which can be protective. Appropriate GA age matched controls lacking both lesions are uncommon.

Chronic villitis (see Chapter 13) has been associated with seizures, neonatal encephalopathy, and cerebral palsy, predominantly in term or near term infants[1,26,28]. The strongest association is with basal ganglia injury[29]. Most studies have found lesions with higher grade inflammation that involves large fetal vessels to have the strongest effect[30]. Romero has reported a specific fetal vascular cytokine signature associated with chronic villitis that may contribute to CNS pathology[12].

Fetal vascular malperfusion (see Chapter 10) has recently been separated into two subgroups, segmental (total) and global (partial). The former, sometimes referred to as "fetal thrombotic vasculopathy," is caused by fetal large vessel thrombi and has been associated with neonatal encephalopathy, stroke, seizures, cerebral palsy, and neuronal injury at autopsy in stillborns[30–34]. The latter, global (partial), is often associated with chronic partial intermittent umbilical cord obstruction and has been linked to cerebral palsy and neuronal injury in stillborns[30,35]. Both subgroups affect predominantly term infants. Mechanisms of CNS injury with fetal vascular malperfusion may include direct embolization of placental thrombi, release of vasoactive mediators from damaged vascular endothelial cells, and diffuse activation of the fetal coagulation cascade.

Maternal vascular malperfusion (see Chapter 7) can have both protective and deleterious effects on the fetal brain, depending on timing and severity. Mild maternal vascular malperfusion can be protective via ischemic preconditioning as discussed above. However, lesions indicative of more extensive and severe maternal vascular malperfusion, particularly villous infarcts, have been linked to microcephaly and developmental delay in extremely low birth weight infants, neuronal damage in stillborns, and cerebral palsy in both term and preterm infants[27,36–38]. Possible pathogenic factors include acute circulatory derangements caused by sudden villous infarction and the profound chronic deprivation of oxygen and metabolites that accompanies severe uteroplacental insufficiency. Severe uteroplacental insufficiency is also seen with maternal floor infarction/massive perivillous fibrin deposition, another maternal vascular lesion associated with neurodisability[39].

Delayed villous maturation (see Chapter 9) has been associated with neonatal encephalopathy and white matter/watershed injury in term infants[29,40]. The proposed mechanism is a decrease in the placental reserve to withstand acute hypoxia in late gestation. This decreased reserve is multifactorial and includes an increased diffusion distance due to decreased vasculosyncytial membranes, increased placental demand due to placentomegaly, increased fetal demand due to macrosomia, and the confounding effects of clinical conditions that often accompany

delayed maturation such as poorly controlled diabetes, obesity, and chronic UC obstruction.

Diffuse villous edema (see Chapter 11) affecting immature intermediate villi is a strong risk factor for cerebral palsy and neurocognitive disorders, as well as death and respiratory distress syndrome, in extremely premature infants[25,27,41]. This association appears to be independent of gestational age and acute chorioamnionitis. The underlying biologic basis is unclear. A direct effect on fetal perfusion or gas exchange due to the edema fluid itself is possible. Alternatively, placental edema may be a biomarker for cardiovascular insufficiency or an excessively immature phenotype for GA in the fetus. Edema in term infants that does not reach the level of hydrops fetalis has received less attention, but a recent study found focal nonspecific terminal villous edema to be the strongest risk factor for significant fetal acidosis at term[42].

Meconium effects (Chapter 19) on the placenta range from mild green staining to accumulation of pigment laden macrophages in chorionic plate stroma and culminate in toxic effects on large fetal vessels (myonecrosis or, rarely, vascular rupture). It is obviously difficult to dissociate the direct effects of meconium from the hypoxic episodes that cause its passage into the amniotic fluid. However, evidence of prolonged exposure, especially myonecrosis, have been correlated with neonatal encephalopathy, neuronal necrosis in stillborns, and cerebral palsy. Potential mechanisms include fetoplacental vasospasm, circulating toxic components of meconium, and the release of inflammatory mediators from damaged myocytes (so called DAMPs).

Retroplacental hemorrhages (see Chapter 8) associated with CNS injury may be separated into arterial hemorrhages (acute or subacute abruptio placentae) and chronic venous hemorrhages occurring at the placental margin (chronic abruption). The former are well known sentinel events causing either total asphyxia (abruptio placentae) or partial prolonged asphyxia (subacute abruptio placentae). Chronic marginal abruption has been found in a few studies to contribute to cerebral palsy in term infants and neuronal necrosis in stillborns[26,35].

Multiple independent placental lesions causing severe placental dysfunction may be the most important of all risk factors for CNS injury. Multiplicity of lesions has shown the strongest magnitude of effect in a diverse group of studies: cerebral palsy in both preterm and term infants, white matter injury and intraventricular hemorrhage in preterm infants, and neuronal necrosis in stillbirths[25,26,34,43]. These effects can either be synchronous and synergistic or metachronous with the earlier lesion sensitizing the CNS for an increased magnitude of effect of the later lesion.

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Chapter

35

Recurrent Pregnancy Loss

Theonia K. Boyd

Recurrent pregnancy loss is due to factors that persist throughout parental reproductive life and compromise multiple pregnancies. Parental – primarily maternal – factors, are poorly understood but thought to often be of immunologic/metabolic etiology. Other causes include anatomic uterine abnormalities and poorly controlled maternal disease processes. Patients with an increased risk of recurrence characteristically exhibit advanced/extensive placental pathology. The same is true of placental disorders with other untoward outcomes, including preterm delivery (see Chapter 31) and neurologic impairment (see Chapter 34).

Previable Recurrent Pregnancy Loss with Placental Correlates

Anatomic Disorders

Abnormal uterine anatomy can predispose to recurrent inadequate embryonic implantation and growth; for example, large submucosal leiomyomas or uterine malformations (e.g., bicornuate uterus, in which the miscarriage rate is highest, having been reported at 60 percent[1]). There are no specific embryoplacental correlates with first trimester losses in this situation, but inadequate fetal and/or placental growth in later gestation may manifest as maternal vascular malperfusion within affected placentas.

Cervical incompetence, due for example to LEEP or cone biopsy, can lead to recurrent mid-gestational previable delivery in up to 70 percent of patients, but drops significantly (5–30 percent) with cerclage[2]. A common clinicopathologic constellation of findings in this setting includes preterm premature membrane rupture, amniotic fluid infection, and "inflammatory" abruption.

Chromosomal Disorders

Parentally inherited aneuploidy (see Chapters 3 and 4), e.g., from unbalanced translocations, or single gene mutations can lead to recurrent early pregnancy failure. The placental phenotype correlates with the specific genetic abnormality. For example, maternally heritable autosomal dominant gestational trophoblastic disease leads to recurrent molar pregnancies due to an NLRP7 gene imprinting mutation, located on chromosome 19q13. Evolution of the phenotype is due to defective placenta-specific imprinting and resulting overexpression of paternally expressed transcripts[3].

Immunologic Disorders

The following conditions, in addition to causing recurrent fetal death after viability, can also lead to recurrent spontaneous abortion.

Chronic histiocytic intervillositis (see Chapters 3 and 15). Chorionic villi are morphologically normal, but the maternal intervillous space is plugged with maternal histiocytes and T cells, usually admixed with fibrin[4]. The risk of pregnancy loss in this patient population is very high (70–80 percent)[4,5]. In a recent multicenter study, despite immunomodulatory therapy (aspirin, prednisone, heparin, hydroxychloroquine; singly or in combination), the risk of recurrent pregnancy loss due to CHI occurred in 33 percent of patients. Concurrent autoimmunity was documented in 30 percent of all patients, underscoring the panoply of organ targets in this patient population[5].

Antiphospholipid antibodies (see Chapters 5 and 7) can, rarely, lead to recurrent spontaneous abortion associated with early onset severe decidual arteriopathy. Decidual tissue fragments may show arteriolar fibrinoid necrosis; in addition, there may be features of maternal malperfusion, such as villous infarction[6]. In a recent multicenter study, immunomodulatory therapy (aspirin, prednisone, heparin, and/or hydroxychloroquine, in addition to anticardiolipids) resulted in a reduction of pregnancy loss from 76 percent in the index pregnancies to 14 percent in subsequently treated gestations[7]. Lupus anticoagulant and anticardiolipin

IgG antibodies were the most prevalent antiphospholipid types, and triple antibody positivity was noted in 45 percent of cases. Co-morbid autoimmune diseases (e.g., thyroiditis, hepatitis, celiac disease) were noted in 13 percent of patients, a theme similar to that seen with CHI[7].

Later Pregnancy Losses (Post-Viability) with Placental Correlates

Chronic histiocytic intervillositis (massive chronic intervillositis; see Chapters 15 and 33) is characterized by a T-cell driven maternal, phenotypically mature histiocytic infiltrate confined to the intervillous space, often with abundant fibrin[4]. Associated conditions include both early and late recurrent stillbirth as well as intrauterine growth restriction in live births. The recurrence risk, absent immunologic intervention, is very high (70–80 percent)[4,5]. Empiric administration of immunomodulatory agents, including low molecular weight heparin, aspirin, and steroids, either alone or in combination, has proven effective in supporting 67 percent of pregnancies to live birth, although preterm deliveries occurred in about half of neonatal births (30 percent of all pregnancies)[5].

Chronic villitis without evidence of infection (villitis of unknown etiology/VUE; see Chapters 13, 33 and 34) is a phenotypically mature maternal T cell/histiocytic response targeted to chorionic villi. Antigenic stimuli (fetal/placental/environmental) that elicit this intrauterine (maternal) host vs. (fetal) graft reaction are unknown. Associated conditions include intrauterine growth restriction, neurodisability in live births, and stillbirth. Diffuse high grade chronic villitis, particularly with concomitant stem villous obliteration and/or extensive intervillous fibrin, is the placental pattern associated with untoward fetal/neonatal outcome, including recurrent late fetal losses, though the greatest risk is with recurrent complications in live births (e.g., IUGR, abnormal neurologic presentation)[8,9]. The baseline rate of recurrent high grade chronic villitis has been reported at 60 percent[8]. Immunomodulatory agents such as aspirin and corticosteroids have been reported to be effective in ameliorating recurrent fetal morbidity and mortality[10].

Maternal floor infarction (MFI)/ Massive perivillous fibrin (MPF) (see Chapters 17 and 33) represent incompletely understood, but may be at least in part immunologically mediated, deposition of intervillous (MPF) and basal (MFI) fibrin-type and matrix-type fibrinoids. MPF is defined by the presence of perivillous fibrin involving >30 percent of the sampled placental disc[12]. MFI is defined as a basal rind of fibrin that encases the basal decidua and chorionic villi along the length of the maternal surface[12]. Specifically implicated causative disorders have included: antiphospholipid antibody family, coagulation pathway mutations, and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. Stillbirth and recurrence rates have been variously reported as high as 30–50 percent and up to 80 percent, respectively[13,15–17].

Maternal vascular malperfusion (see Chapters 7 and 33) is rarely a cause of unexplained fetal demise in developed countries, since routine antenatal surveillance identifies at-risk fetuses. In under-resourced countries, however, maternal vascular malperfusion remains a primary cause of intrauterine demise. Underlying maternal disorders are broadly classified into those mediated by hypertension and those mediated by the effects of maternal autoimmunity[18,19].

Recurrent pregnancy loss occurs with unmodifiable or treatable but unmodified disease; or in resource-poor societies without the capacity for preterm intervention in high risk pregnancies[20].

Diabetes-associated pregnancy losses (see Chapters 9 and 33) can be recurrent if affected mothers have so-called "brittle" disease (unstable glucose control), disease that resists treatment, or who live in societies without the capacity for detection and/or intervention. Diabetes leads to recurrent pregnancy loss[21] when mediated by specific mechanisms which include maternal vascular malperfusion, fetal vascular malperfusion, fetal hypertrophic cardiomyopathy, and complications of fetal macrosomia.

Abnormal uterine anatomy can predispose to recurrent pregnancy complications, including recurrent pregnancy loss following gestational viability[1].

Etiologies include:

1) maternal vascular malperfusion related to implantation overlying large submucosal leiomyomas with limited arteriolar uteroplacental perfusion;
2) fetal vascular malperfusion as a consequence of space constraint-induced umbilical cord compression (e.g., bicornuate uterus with bilobate placentation within the uterine horns and velamentous cord insertion between the lobes); and

3) placenta accreta/percreta (e.g., due to C-section site implantation) complicated by uterine rupture, placental abruption, and/or fetal hemorrhage.

Fetal vascular malperfusion (see Chapters 10 and 33), though a common cause of late fetal demise, is almost always sporadic in etiology. When recurrent, the responsible mechanisms persist from one pregnancy to another.

Recurrent fetal vascular malperfusion-mediated causes may include:

1) maternal or fetal thrombophilia (maternal antiphospholid antibodies, fetal protein C or S deficiency);
2) umbilical cord abnormalities recurring as a consequence of maternal vascular malperfusion (narrow cord, abnormal insertion, oligohydramnios-induced compression);
3) diabetes-associated fetal thrombosis and/or delayed villous maturation; and
4) cord compression due to abnormal uterine anatomy.

Finally, there are rare case reports of successive pregnancy losses due to recurrent umbilical hypercoiling or stricture (see Chapter 16)[22], suggesting a maternal/genetic component among the factors that influence ultimate cord geometry.

Multiple chorangioma syndrome (see related *giant chorangioma/extensive multifocal* chorangiomatosis; Chapters 9 and 33) is a very rare recurrent condition, characterized by hundreds of chorangiomas ranging from a few millimeters to several centimeters in size[23]. Its genetic basis has not been established, though increased expression of angiogenic growth factors (e.g., angiopoietin) has been demonstrated[24].

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Appendix 1: Common Clinical and Biologic Abbreviations

AROM = artificial rupture of membranes
ART = artificial reproductive technology
BPP = biophysical profile
CAOS = chronic abruption oligohydramnios sequence
CBC = complete blood count
CMV = cytomegalovirus
CNS = central nervous system
DAMP = damage associated molecular pattern
D&C = dilatation and curettage
EPL = early pregnancy loss
EVT = extravillous trophoblast
ETOH = ethanol/alchohol
FGR = fetal growth restriction
GA = gestational age
GBS = group B streptococcus
GTD = gestational trophoblastic disease
HELLP = hemolysis-elevated liver enzymes-low platelets
hCG = human chorionic gonadotropin
IPB = indicated preterm birth
IUFD = intrauterine fetal demise
IUGR = intrauterine growth restriction
IVF = in vitro fertilization
LEEP = laser electrical excision procedure
LGA = large for gestational age
LSD = lysosomal storage disorder
MAP = morbidly adherent placenta
MHC = major histocompatibility complex
MRI = magnetic resonance imaging
MSF = meconium stained fluid
NIHF = nonimmune hydrops fetalis
NRBC = nucleated red blood cell
PCR = polymerase chain reaction
PET = preeclampsia/toxemia
PFD = pulsed flow Doppler
PNC = prenatal care
PPH = postpartum hemorrhage

PROM = premature rupture of membranes
PPROM = preterm premature rupture of membranes
RPH = retroplacental hemorrhage/hematoma
SGA = small for gestational age
SNP = single nucleotide polymorphism
SPB = spontaneous preterm birth
SUA = single umbilical artery
TAPS = twin anemia polycythemia sequence
TORCH = toxoplasma-other-rubella-cytomegalovirus-herpes simplex
TRAP = twin reversed arterial perfusion
TTTS = twin twin transfusion syndrome
UC = umbilical cord
US = ultrasound
VUE = villitis of unknown etiology

Appendix 2: Gross Examination

Pre-analytic variables

Proper gross examination of the placenta requires communication, verbal or written, between pathologist and clinician both in terms of standing policies and data available with the submission. Most experts believe that examination of the placenta prior to fixation is optimal. However, fixation in an adequate amount (at least 2–3 volumes) of formalin is an acceptable alternative, especially if transportation and storage issues are involved. If placentas are examined fresh, prompt refrigeration is essential. Prolonged refrigeration is usually not a serious problem and adequate histology can be obtained as long as 5–7 days after delivery.

Pathologists need to understand the relevant clinical issue(s) before undertaking gross examination of the placenta. Gestational age, gravidity and parity, relevant maternal obstetric history, the presence of underlying maternal disease, fetal weight, neonatal Apgar scores, and the specific questions or reasons for submission are the minimum information required for a proper placental evaluation.

Examining the gross specimen (singleton births)

Methods may vary. The procedure we use is outlined below.

1. Employ universal precautions for preventing the transmittal of blood borne pathogens with every specimen.
2. Work in a large, well lit, and well ventilated space with absorbent tissue pads, a scale, a large centimeter ruler, scissors, smooth forceps, a large knife, scalpel or razor blades, and small containers of formalin for the fixation of untrimmed tissue blocks.
3. Remove the placenta from container, drain, and gently remove loose blood clots over an appropriate biohazard waste receptacle.
4. Place the placenta on the cutting surface with the membranes in anatomic position and the maternal surface down.
5. Prepare two membrane rolls, each wrapped around a small piece of marginal placenta and place in the small formalin container. Trim the remaining membranes from the placental margin.
6. Measure, remove, and section the umbilical cord. Place two sections taken from areas 1/3 and 2/3 of the distance from free end to insertion in the small formalin container.
7. Measure the longest axis of the placental disc, the orthogonal diameter, and the shortest distance from the margin to the cord insertion site.
8. Weigh the placenta (following removal of the umbilical cord and membranes).
9. Inspect the maternal and fetal surfaces and make parallel cuts at 1–2 cm intervals starting at the maternal surface and extending to, but not through, the fetal surface.
10. Obtain three nonmarginal full thickness blocks including one from directly underneath the umbilical cord insertion site (each approximately 3–4 cm in width) by extending the parallel cuts through the fetal surface using forceps and scissors. Place in formalin.
11. Return the sectioned placenta to its original container and fill with formalin.

12. Trim and block final tissue sections into cassettes 4–6 hours or more after initial fixation in formalin (five cassettes: umbilical cord sections, membrane rolls, and three parenchymal sections are adequate for most cases).

Describing the gross specimen

The gross description of the placenta should be concise, consistent from case to case, and include all of the following synoptic elements:

- Presence or absence of fixative
- Trimmed weight of the placental disc
- Length, color (yellow, green, red), and distance from the nearest margin of umbilical cord
- Degree, direction, and severity of umbilical cord coiling (Degree = number of diagonal twists in a representative 10 cm segment, Direction = left when twists run from upper left to lower right or right when twists run from upper right to lower left, Severity = presence or absence of indentations between coils)
- Type of membrane insertion (marginal versus circumvallation; partial or complete)
- Completeness of membranes
- Point of membrane rupture (shortest distance to the placental margin)
- Color of the fetal surface (blue, green, brown)
- Shape abnormalities (accessory lobes, multilobation, irregular contour, marginal atrophy)
- Disruption or incompleteness of the maternal surface
- Specific abnormalities on cut surface (cysts, masses, hemorrhages abnormal firmness of parenchyma or basal plate)

Selected aspects of grossing placentas from multiple gestations

General:

The first responsibility of the pathologist is to separate monochorionic placentas from dichorionic placentas. Chorionicity should be established before dissection by evaluation of the dividing membrane and then documented by histologic section in the form of either a dividing membrane roll or a T-section.

Dichorionic means two placentas: each placenta is a separate developmental, structural, and functional entity and should be physically separated from its partner (even if intimately fused to it), individually weighed, and independently evaluated at gross examination. Dichorionic placentas virtually never have twin-twin anastomoses.

Monochorionic means one placenta; it should not be separated and is weighed as a single disc. The approximate percentage of the chorionic plate occupied by fetal vessels emanating from each umbilical cord should be estimated. Virtually all monochorionic placentas have twin-twin anastomoses, but the number and nature of the anastomoses varies considerably and can be evaluated at the time of gross examination (see below).

Specific techniques:

1. Completely separated twin placentas and twin placentas connected by membranes alone are "separate, dichorionic diamnionic" and each can be processed as a singleton. A dividing membrane role is not necessary.
2. Single versus fused twin placentas can best be distinguished by tugging firmly on the dividing membrane in the direction of each umbilical cord. A true dividing membrane is anchored on both sides and will not peel off the placenta. Disruption of the surface amnion can mimic a dividing membrane, but will always peel away with traction. Holding the dividing membrane up, nick each side with a scalpel blade and peel the nicked edge downward with fine forceps. If the dividing membrane is translucent and shows only two layers after peeling, the placenta is monochorionic. If the dividing membrane is opaque and shows three layers after peeling, the placentas are fused and dichorionic. If fused and dichorionic, turn the placenta over and proceed to separate the two placentas by firm manual blunt dissection, weighing each disc separately.

3. Monochorionic twin placentas generally have vascular communications. In most cases, this communication consists of both surface artery to artery anastomoses and deep parenchymal connections (artery-artery, vein-vein, and/or artery-vein).
We screen for large deep anastomoses by air injection as follows. Select the placenta with the thinner umbilical cord (possible donor twin). In sequential fashion the two to three major arteries (arteries go over veins) are then proximally ligated and distally injected with air using a plastic syringe with a 19 gauge needle inserted at a point just after their emergence from the umbilical cord insertion site. Unobstructed major anastomoses will allow air to pass freely to the opposite placenta. If the transmitted air appears in a vein having no surface continuity with the injected artery, a deep artery-vein anastomosis has been confirmed. If the first two to three injections are negative, the placenta is turned around and the major arteries of the second placenta are injected. If all injections are negative after this 5–10 minute exercise, clinically significant anastomoses are largely excluded. More rigorous dye injection techniques may be applicable for selected cases.

Appendix 3: Placental Weights: Means, Standard Deviations, and Percentiles by Gestational Age

(Appendix 2A from Placental pathology, FT Kraus, RW Redline, DJ Gersell et al, American Registry of Pathology. 2004)

Percentiles, Means, and Standard Deviations for Placental Weights by Gestational Age[a]

Gestational Age(weeks)	N[b]	Mean	SD	Percentile								
				3	5	10	25	50	75	90	95	97
22	19	189	89		99	107	130	166	206	285	499	
23	16	190	41			127	168	188	208	262		
24	16	190	42			128	157	192	222	252		
25	26	197	70		105	128	153	184	216	299	400	
26	22	226	100		107	138	179	200	259	281	570	
27	22	240	77		119	130	166	242	310	332	381	
28	41	223	66	103	128	140	173	214	261	321	361	371
29	37	269	96	124	135	161	214	252	309	352	496	629
30	42	324	88	185	190	208	269	316	374	433	502	570
31	57	314	105	142	152	175	246	313	360	417	479	579
32	69	325	77	161	214	241	275	218	377	436	461	465
33	117	351	83	190	224	252	286	352	413	446	475	504
34	160	381	54	221	260	283	322	382	430	479	527	558
35	260	411	99	232	250	291	344	401	471	544	600	626
36	538	447	110	270	291	320	369	440	508	580	628	679
37	1103	467	107	303	324	349	390	452	531	607	660	692
38	2469	493	103	320	335	365	420	484	560	629	675	706
39	3932	500	103	330	350	379	426	490	564	635	683	713
40	4114	510	100	340	360	390	440	501	572	643	685	715
41	1982	524	100	358	379	403	452	515	583	655	705	738
42	321	532	99	370	388	412	460	525	592	658	700	771

Placental mean trimmed weights and percentiles by gestational age and fetal-placental weight ratios by gestational age. Data is compiled from 15,463 deliveries. The patient mix included a diversity of ethnic, racial, and demographic groups at the Baystate Medical Center, Springfield, Massachusetts. Placentas were weighed fresh, after removal of cords and membranes. Placentas From intrauterine death or obvious growth dysregulation (such as triploidy) and incomplete placentas were excluded.

Appendix 4: Fetal-Placental Weight Ratios, Means, Standard Deviations, and Percentiles by Gestational Age

(Appendix 2c from Placental pathology, FT Kraus, RW Redline, DJ Gersell et al, American Registry of Pathology. 2004)

Fetal-Placenta Weight Ratio Percentiles by Gestational Age[a]

Gestational Age(weeks)				Percentile								
	N[b]	Mean	SD	3	5	10	25	50	75	90	95	97
22	19	2.9	0.8		1.0	1.0	2.0	2.4	3.6	3.9	4.3	
23	16	3.3	0.7				2.4	2.9	3.6	4.5		
24	16	3.4	1.0				2.0	2.6	4.0	4.6		
25	26	4.0	1.4		1.7	2.2	3.2	3.8	4.6	6.0	7.4	
26	22	4.1	1.2		2.1	2.8	3.4	3.7	4.8	5.2	7.7	
27	22	4.5	1.1		2.6	3.0	3.3	3.6	4.5	6.0	7.1	
28	41	4.8	1.0	2.3	2.5	3.6	3.9	4.2	4.7	6.5	6.6	6.9
29	37	5.2	1.4	1.9	2.5	3.7	4.4	5.0	5.7	7.5	8.0	9.2
30	42	5.2	1.1	2.7	3.1	3.6	4.5	5.1	5.8	6.8	6.9	7.6
31	57	5.5	1.1	3.3	4.1	4.4	4.7	5.4	6.2	6.9	7.3	8.2
32	69	5.9	1.2	3.2	4.1	4.4	5.0	5.8	6.8	7.7	7.9	8.4
33	117	6.0	1.1	4.3	4.5	4.7	5.2	6.0	6.6	7.7	8.2	8.7
34	160	6.2	1.0	4.4	4.7	5.0	5.5	6.1	6.7	7.5	7.9	8.2
35	260	6.4	1.2	4.5	4.7	5.0	5.6	6.3	7.2	8.0	8.6	9.1
36	538	6.6	1.1	4.8	4.9	5.3	5.8	6.4	7.3	8.1	8.4	8.8
37	1103	6.8	1.1	4.9	5.1	5.4	6.0	6.7	7.4	8.2	8.8	9.1
38	2469	6.9	1.1	5.1	5.2	5.6	6.1	6.8	7.5	8.3	8.9	9.2
39	3932	7.1	1.1	5.2	5.4	5.7	6.3	7.0	7.7	8.5	9.1	9.4
40	4114	7.2	1.1	5.3	5.5	5.8	6.4	7.1	7.9	8.6	9.1	9.5
41	1982	7.2	1.1	5.4	5.6	5.9	6.5	7.1	7.8	8.6	9.1	9.4
42	321	7.1	1.1	5.3	5.5	5.9	6.4	7.1	7.8	8.5	8.9	9.1

Placental mean trimmed weights and percentiles by gestational age and fetal-placental weight ratios by gestational age. Data is compiled from 15,463 deliveries. The patient mix included a diversity of ethnic, racial, and demographic groups at the Baystate Medical Center, Springfield, Massachusetts. Placentas were weighed fresh, after removal of cords and membranes. Placentas From intrauterine death or obvious growth dysregulation (such as triploidy) and incomplete placentas were excluded.

Appendix 5: Mean Weights and Percentiles for Twin Placentas

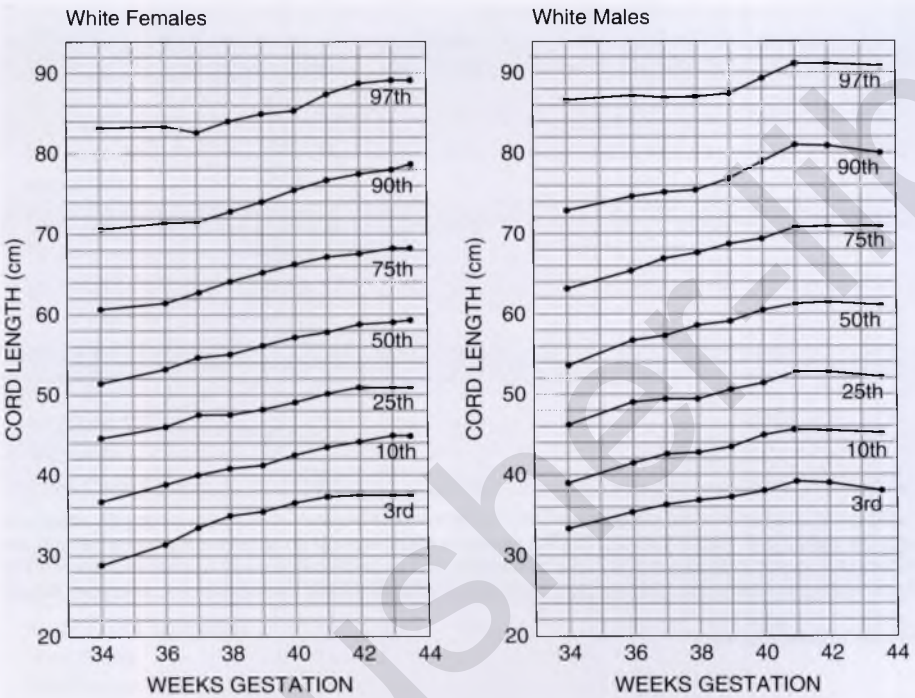
Mean Weights and Percentiles for Twin Placentas[a]

Gestational Age (weeks)	90th Percentile	75th Percentile	Mean Twin Placental Weight (g)	25th Percentile	10th Percentile	Number Of Cases
19	263	239	212	185	161	2
20	270	245	218	190	166	3
21	286	260	231	202	176	2
22	310	282	251	219	791	5
23	343	311	276	241	210	2
24	382	346	307	267	232	3
25	426	386	341	297	257	5
26	475	430	380	330	284	4
27	528	478	421	365	314	8
28	584	527	464	401	345	7
29	641	579	509	439	377	12
30	700	631	554	478	409	17
31	758	683	600	516	441	13
32	815	734	644	554	472	29
33	870	783	687	590	503	27
34	923	830	727	624	531	53
35	971	873	764	656	558	52
36	1014	912	798	684	582	66
37	1051	945	827	708	602	58
38	1082	972	850	728	619	54
39	1105	993	868	743	631	38
40	1118	1005	879	753	639	47
41	1123	1009	882	756	642	12

[a] Table 2 from Pinar H, Sung CJ, Oyer CE, Singer DB. Reference values for single ton and twin placental weights. Pediatr Pathol Lab Med 1996;16:904.

Table of mean trimmed weights and percentiles for twin placentas ages. Both dichorionic and monochorionic placentas were included, with no distinction between the two. The same pathologic and clinical exclusions as in Appendix 3 apply to this group as well. Also excluded were triplets and higher orders of multiple gestation, and twins discordant for weight.

Appendix 6: Umbilical Cord Length by Gestational Age



A: Umbilical cord length by gestational age in white males from 34 to 43 weeks in the United States (8). (Fig. 1 from Mills JL, Harley EE, Moessinger AC. Standards for measuring umbilical cord length. Placenta 1983;4:423–6.)

B: Umbilical cord length by gestational age in white females in the United States. Male cords are significantly longer ($p<0.0001$). Cord lengths vary widely from shortest to longest in the same gestational age groups. These data, like those in Appendix 6, were compiled from the collaborative Perinatal Project.

Measurement of a short umbilical cord is only valuable when the entire cord can be accounted for. Portions of a cord sent for blood gas analysis often result in a false impression of a short cord based on measurement in the pathology laboratory. Umbilical cord length greater than 70 cm is considered excessively long and is associated with increased morbidity and mortality (1). Cords greater than 90 cm are associated with adverse outcome more often than not. (Fig.2 from Mills JL, Harley EE, Mosseinger AC. Standards for measuring umbilical cord length. Placenta 1983;4:423–6.)

Appendix 7: Umbilical Cord Coiling Index

Distribution of Cord Coil Index in 120 Consecutive Unselected Pregnancies

Cord Coil Index	N[c]	(%)
0.0–0.049	2	(1.7)
0.05–0.099	7	(5.8)
0.1–0.149	15	(12.5)
0.15–0.249	20	(16.7)
0.25–0.299	36	(30.0)
0.3–0.349	16	(13.3)
0.35–0.399	14	(11.7)
0.4–0.449	5	(4.2)
0.4–0.449	3	(2.5)
0.45–0.499	2	(1.7)
Total	120	1(00)

Distribution of cord coil index in 120 consecutive unselected pregnancies from the Permanente Medical Group. There is normally about one complete twist(coil)/5 cm of cord. The normal coil index is 0.2 coils/cm. The variations in coil index in an unselected group of patients are tabulated above. An over coiled cord(OCC) has an index equal to 0.3 coils or more/cm, and an under coiled cord(UCC) has an index of 0.1 or less principal clinical fetal death, intolerance to labor, intrauterine growth restriction, chorioamnionitis, thrombosis of chronic plate vessels or cord, and cord stenosis.

[b] Table 2 from Machin GA, Ackerman J, Gilbert-Barness

Pediatr Dev Pathol 2000;3:465

'N = number of cases

Appendix 8: Placental Histologic Features in Stillbirth by Time Interval before Delivery

Histologic Feature	Time of Fetal Death Before Delivery (Cases with Histologic Feature)						
	<6 h (N=15)	<6 24 h (N=13)	<24-48 h (N=5)	<2-7d (N=5)	7-14d (N=4)	14-28d (N=4)	>28d (N=5)
Intravascular karyorrhexis	0%	85%	100%	100%	100%	100%	100%
Extensive villous fibrosis	0%	0%	0%	20%	50%	100%	100%
Stem vessel luminal abnormalities							
Multifocal (10–25% of stem villi)	0%	0%	0%	60%	100%	50%	0%
Extensive (>25% of stem villi)	0%	0%	0%	20%	0%	50%	100%
Cord stromal necrosis	7%	31%	0%	60%	75%	67%	100%
Cord vascular necrosis	0%	0%	0%	0%	50%	33%	100%
Stromal "dusty" calcification	7%	0%	20%	40%	75%	75%	40%
Trophoblast basement membrane calcification/ thickening	13%	0%	0%	40%	100%	50%	40%

[a] Table 2 from Genest DR. Estimating the time of death in stillborn fetuses: II Histologic evaluation of the placenta: a study of 71 stillborns. Obstet Gynecol 1992;80:587.

Appendix 9: Means and Standard Deviations for Placental Weights and Dimensions, Birth Weights, and Fetoplacental Weight Ratios by Gestational Age (UH Cleveland Medical Center, 2006–2015, N=6948, unpublished data)

Gestational Age Range (wks)		Placental Weight (gm)	Length/ Maximum Diameter (cm)	Breadth/ Minimum Diameter (cm)	Length minus Breadth (cm)	Calculated Average Thickness (cm)		Birth Weight (gm)	Fetoplacental Weight Ratio
23-23.9 N=42	Mean (SD)	157 (43)	14.8 (2.6)	11.8 (1.6)	3.0 (2.5)	1.2 (0.3)	N=20	583 (131)	4.0 (1.5)
24-24.9 N=51	Mean (SD)	172 (63)	14.4 (2.0)	12.1 (2.0)	2.2 (1.9)	1.3 (0.5)	N=24	665 (86)	4.3 (1.0)
25-25.9 N=63	Mean (SD)	181 (71)	14.9 (2.0)	12.5 (1.9)	2.4 (2.1)	1.3 (0.4)	N=37	764 (123)	4.6 (1.2)
26-26.9 N=56	Mean (SD)	194 (56)	15.5 (2.5)	13.0 (1.9)	2.5 (1.9)	1.3 (0.3)	N=36	840 (206)	4.5 (1.3)
27-27.9 N=45	Mean (SD)	202 (62)	14.9 (1.8)	13.0 (2.1)	1.9 (1.6)	1.3 (0.3)	N=17	940 (265)	4.8 (1.1)
28-28.9 N=77	Mean (SD)	246 (70)	16.1 (2.3)	13.6 1.9)	2.5 (1.7)	1.5 (0.4)	N=48	1159 (245)	4.9 (1.3)
29-29.9 N=76	Mean (SD)	248 (80)	16.0 (2.1)	13.6 (1.9)	2.3 (1.6)	1.5 (0.5)	N=40	1336 (505)	6.1 (3.8)
30-30.9 N=106	Mean (SD)	297 (118)	17.1 (2.6)	14.8 (2.3)	2.3 (1.9)	1.6 (1.2)	N=69	1540 (383)	5.7 (1.7)
31-31.9 N=104	Mean (SD)	286 (74)	17.0 (2.5)	14.6 (2.1)	2.5 (1.8)	1.5 (0.3)	N=67	1595 (370)	5.8 (1.3)
32-32.9 N=152	Mean (SD)	319 (82)	17.5 (2.1)	15.1 (1.8)	2.5 (1.8)	1.5 (2.1)	N=107	1894 (433)	6.0 (1.4)
33-33.9 N=194	Mean (SD)	348 (95)	17.9 (2.4)	15.4 (2.0)	2.5 (2.0)	1.6 (0.4)	N=130	2033 (392)	6.1 (1.3)
34-34.9 N=335	Mean (SD)	377 (88)	18.4 (2.4)	15.8 (2.0)	2.6 (2.1)	1.7 (0.4)	N=261	2232 (400)	6.0 (1.0)
35-35.9 N=375	Mean (SD)	403 (102)	18.6 (2.5)	16.0 (2.1)	2.6 (2.6)	1.7 (0.4)	N=328	2447 (440)	6.3 (1.4)
36-36.9 N=515	Mean (SD)	419 (106)	19.2 (0.4)	16.4 (2.1)	2.8 (2.6)	1.7 (0.4)	N=465	2687 (462)	6.6 (1.3)
37-37.9 N=552	Mean (SD)	430 (110)	19.2 (2.7)	16.6 (2.3)	2.7 (2.5)	1.8 (0.4)	N=497	2908 (585)	6.9 (1.4)
38-38.9 N=1053	Mean (SD)	434 (109)	19.4 (2.5)	16.7 (2.2)	2.8 (2.4)	1.7 (0.5)	N=944	3063 (507)	7.3 (2.4)
39-39.9 N=1406	Mean (SD)	460 (151)	19.7 (2.6)	17.0 (2.1)	2.8 (2.3)	1.8 (0.5)	N=1257	3219 (503)	7.2 (1.6)
40-40.9 N=1249	Mean (SD)	481 (131)	20.0 (2.6)	17.3 (2.2)	2.7 (2.3)	1.8 (0.8)	N=1094	3405 (459)	7.3 (1.2)
41-41.9 N=497	Mean (SD)	495 (109)	20.4 (2.9)	17.4 (2.3)	3.0 (2.9)	1.8 (0.4)	N=450	3508 (463)	7.4 (3.0)

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This concise and comprehensive resource is vital for the pathologist faced with providing accurate, timely, and clinically useful diagnoses for placentas, products of conception, and gravid hysterectomies. Combining the pathologic, research, and clinical expertise of a diverse group of editors and authors from centers of excellence for placental pathology, this book:

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