

THE NORMAL PLACENTA

Immune Anatomy and Function

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The fact that the semi-allogeneic conceptus can develop for 9 months, most commonly without harm, shows that protective mechanisms must exist that permit its survival. These mechanisms are so finely tuned or so locally confined that the immune rejection of the conceptus is prevented while maintaining the mother's ability to fight infection. One consequence of this immune silence may be the late onset of systemic manifestations of intrauterine infections, such as chorioamnionitis. This silence may be part of the complexity that has surrounded issues of vertical transmission of infectious disease in general and HIV in particular.

NORMAL PLACENTAL FUNCTION

In basic physiologic terms, the placenta's function is to exchange nutrients. Factors determining net fetal nutrient transfer include "... maternal and fetal blood flows, the pattern of placental perfusion, the surface, thickness and physicochemical properties of the placental membrane, the metabolic activity of the placenta, the various mechanisms of transfer which are available (e.g., diffusion, carrier mediated transfer, active transfer), and *regional differences in placental histology and function* [our italics]."⁶ Basic normal anatomy of the pregnant uterus, the placenta and implantation site, and the terminal (nutrient exchange) villus are presented in Figures 1, 2, and 3. (Refer to Popek's article elsewhere in this issue for additional materials on villous anatomy and pathology.)

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Figure 1. Human chorionic sac containing a 13-week-old fetus. Smooth and villous areas of the chorion (actual size) shown. (*From Moore KL, Persaud TVN: The Developing Human: Clinically Oriented Embryology, ed 5. Philadelphia, WB Saunders, 1993, pp 116–117; with permission.*)

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Figure 2. Sagittal section of a gravid uterus at 22 weeks. The relation of the placenta and fetal membranes to each other and to the regions of the decidua are shown. The fetus has been removed, and the amnion and smooth chorion have been cut and reflected to show their relationship to each other and the decidus parietalis. (*From Moore KL, Persaud TVN: The Developing Human: Clinically Oriented Embryology, ed 5. Philadelphia, WB Saunders, 1993, pp 116–117; with permission.*)

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Figure 3. A full-term placenta section showing: (1) the relation of the villous chorion (fetal part of placenta) to the decidua basalis (maternal part of placenta), (2) the fetal placental circulation, and (3) the maternal placental circulation. Maternal blood flows into the intervillous space in funnel-shaped spurts. The main exchange of material between the mother and embryo/fetus occurs through the branch villi. The inflowing arterial blood pushes venous blood out into the endometrial veins, which are scattered over the entire surface of the decidua basalis. Note that the umbilical arteries carry poorly oxygenated fetal blood to the placenta and that the umbilical vein carries oxygenated blood to the fetus. Note that the cotyledons are separated from each other by decidual septa, projections of the maternal portion of the placenta (decidua basalis). Each cotyledon consists of two or more main stem villi and their many branches. Only one stem villus is shown in each cotyledon, but the stumps of those that have been removed are indicated. (*From Moore KL, Persaud TVN: The Developing Human: Clinically Oriented Embryology, ed 5. Philadelphia, WB Saunders, 1993, pp 116–117; with permission.*)

Changes in the physical barrier function of the placenta may not only affect fetal nutrient availability but also facilitate transplacental transmission of infectious agents, including HIV. The marked regional variation within this organ may have complicated attempts to study the likely nonuniform placental barrier to congenital HIV infection.

Nonvillous Trophoblast and the Decidua and Uteroplacental Circulation

To establish pregnancy, the trophoblast must anchor to and invade the decidualized endometrium,²⁶ and the uterine vasculature must be both destroyed and remodeled to establish a nutrient supply line from

the maternal to the fetoplacental circulation.²⁵ Uterine vascular remodeling begins before trophoblast arrival at the artery wall, and in the absence of local trophoblast, the implication is that some aspects of vascular remodeling (including marked endothelial hypertrophy disrupting the normal smooth contour of the vessel lumen and increasing attenuation of the media to the point that the lining endothelium is surrounded only by a layer of reticular or collagen fibers⁶³) may be initiated by maternal (rather than fetoplacental) signals. Nontrophoblast-dependent (and potentially preimplantation) uterine vascular changes may affect dynamics of local (intrauterine) HIV carriage.

The trophoblast epithelial cell is the principal intermediary between the maternal and placental tissues in the basal plate and the principal barrier separating the maternal and fetoplacental circulations at the villous level. Recent reviews summarize current data regarding regulation and modulation of trophoblast functions.⁵⁶ In the basal plate, the trophoblasts (from the earliest days of gestation) establish a sluggish maternal capillary pool that bathes the conceptus with low but real flow. It has recently been suggested that endovascular trophoblast plugs completely occlude the maternal circulation during spiral arterial conversion, acting to protect the conceptus from maternal arterial circulatory pressure until implantation is well-established^{40, 41}; precocious maternal arterial perfusion of the intervillous space would, in this model, be a possible cause of early pregnancy loss.⁴² The issue of whether the entire period of embryogenesis occurs without any direct contact with the maternal circulation is directly relevant to questions of early HIV vertical transmission, but at present may not be completely resolved. A consensus may agree that focal plugs do not completely occlude maternal circulation⁵⁴; an early, low flow, capillary type intervillous circulation is likely.⁵³

Retrograde trophoblast extension into spiral vessels is often described as proceeding in two waves, the first completed by the end of the first trimester and the second by the early second trimester,⁶³ by which time invasive trophoblasts penetrate the superficial one third of the myometrium. Trophoblast endovascular invasion is likely a more continuous single process, with a more open-ended completion date, extending on occasion into the third trimester. This invasion may be relevant if active maternal tissue remodeling contributes to viral activation or local availability. Complete conversion includes re-endothelialization of the maternal artery. The conversion is accompanied by a placental bed monocyte/macrophage presence, the distribution of which has been shown to differ in pathological pregnancies.⁶¹ Decidual macrophages account for 35% to 40% of the decidual leukocyte population. It is assumed that they function locally as antigen presenting cells, and are commonly closely associated with extravillous trophoblast.¹⁷ Their primary role may be the phagocytosis of remodeling debris, or as immunoregulatory (but noninflammatory) down-regulators of inflammation, possibly via production of interleukin (IL) 10.¹⁷ Converted uteroplacental vessels, no longer responsive to vasomotor stimuli,²² empty into the

intervillous space. After trophoblast remodeling of spiral vessels, the intervillous space is a high-capacitance, low-resistance system (blood pressure of approximately 10–12 mm Hg). There is decreased trophoblastic invasion of decidua at the placental margins compared with the center, with less extensive uteroplacental vascular conversion.¹² Thus the placental margins are less well perfused, less functional zones that contribute little to fetal nutrition or potentially to viral transfer.

Invasive trophoblast may be most clearly and, more important, functionally distinguished from villous trophoblast by its low level expression of a major histocompatibility antigen, histocompatibility locus antigen (HLA)-G. Locally in the placental bed, low level expression of alloantigens on extravillous trophoblast may elicit local production of growth-enhancing cytokines. Such expression may also stimulate production of noncytotoxic antipaternal antibodies and recruitment of local suppressor cells. Additional (nonimmune) functions of the histocompatibility locus antigens may include roles in cell-to-cell recognition, cell positioning, adhesion and contact inhibition, and in influencing peptide hormone binding, including insulin and EGF; therefore, maternally generated antipaternal major histocompatibility locus (MHC) antibodies could regulate trophoblast proliferation.⁴⁰ Cytokines, and therefore the local infectious status or the general immune state of the mother, would influence the invasive trophoblast. Invasive trophoblast does express tumor necrosis factor (TNF)- α ,¹⁹ transforming growth factor (TGF)- α ,³⁹ IL-1,⁷⁹ and TGF- β ,^{52, 76} the proto-oncogene product *c-erb* B2,⁴³ as well as receptors for M-CSF⁴⁴ and IL-1.⁷⁹ TNF- α , TGF- β , and IL-1 are also present within decidual stromal cells. Complement regulatory proteins (including CD46 and decay-accelerating protein) are expressed on extravillous trophoblast, which would effectively negate complement mediated attack at the fetomaternal interface arising through either maternal antibody attack or low level complement activation due to local tissue restructuring.¹⁷ Placental bed macrophages are reported to express IL-1⁷⁹ and the receptor for M-CSF.⁴⁴ Decidual IL-2 expression³⁵ and TNF- α (localized to the macrophage-derived foam cells of atherotic uteroplacental vessels) is seen in preeclamptic, compared with uncomplicated, pregnancies.

Other factors that may affect trophoblast-uterine interactions and are modifiable by immune-associated stimuli include the extracellular matrix, alteration of integrin expression,^{4, 20} secretion of proteinases, including urokinase-type plasminogen activator and various metalloproteinases, and associated inhibitors (plasminogen activator inhibitors PAI-1 and PAI-2, gelatinases, and tissue inhibitors of metalloproteinases [TIMPs]).^{9, 33, 50}

The Villous Trophoblast Barrier and Villi

The villous trophoblast provides a continuous epithelial lining to the intervillous blood space, and its growth parallels the arborization of the villous tree. So-called "primary villi" are simple columns of

cytotrophoblast that develop from the cytotrophoblastic shell. Mesodermal invasion into (or in situ differentiation within) primary villi leads to "secondary villi." The appearance of blood vessels transforms these into "tertiary villi."¹¹ The transformation from primary to tertiary villi is well established by the end of the fifth week of gestation, when a beating embryonic heart begins to pump nucleated erythrocytes from the yolk sac throughout the villous circulation. At this point, the maternal and fetoplacental circulations are in remote proximity, separated at this time by the relatively broad barrier of a bilayered epithelial surface (syncytio- and cytotrophoblast) plus the stroma intervening between the villous surface and the relatively centrally located fetoplacental vessels. Villous macrophages (Hofbauer cells) are numerous throughout gestation (40% of stromal cells),³² although at term they may be inconspicuous. Early villi arborize by mesenchymal invasion of syncytial sprouts,⁷ which may be deported into the maternal circulation. Villi originally develop over the entire sphere of the conceptus but atrophy over the extraplacental membranes by the end of the first trimester. Whether this involutational process ever even transiently impairs the integrity of the villous trophoblast barrier is not known.

Trophoblasts have long been proposed to modulate maternal immune function via secreted immunomodulator factors. Recently, in vitro cultured trophoblasts have been described to secrete factors that increase both the amount of antibody produced and the proportion of "asymmetric antibodies" synthesized; these factors also reduce proliferation of antibody-producing cells. Asymmetric antibodies (glycosylated in only one of the Fab regions, sterically hindering antibody-antigen binding) function as "blocking antibodies." Once asymmetric antibodies reach 30% proportions (a proportion reached under the experimental conditions), complement activation, opsonization, and phagocytosis are impaired.¹⁰ Another local immunosuppressive mechanism may be the production of high local levels of soluble Fc gamma-receptors (by either extravillous or villous trophoblast), which may reduce mitogen-induced lymphoproliferation.¹ Human placenta also expresses receptors for M-CSF, G-CSF, GM-CSF, TNF and IFN- γ .¹⁷ Cytokines such as M-CSF, GM-CSF, and IL-3 have been shown to augment placental growth.⁶⁷ Trophoblast also expresses Fc-gamma receptors, primarily of the type 3 subtype. In the first trimester, Fc-gamma receptors can be seen on both first trimester syncytio- and cytotrophoblast and at the syncytio- and cytotrophoblast junction; by the latter half of pregnancy, Fc-gamma receptors are mainly confined to syncytiotrophoblast with transplacental IgG transport occurring via pinocytosis.⁸⁰

Trophoblast forms a sophisticated selective barrier and transfer system; under normal conditions, the lack of HLA antigen expression on syncytiotrophoblast should preclude syncytiotrophoblast from allogeneic immune-mediated injury.⁸ No detectable class I antigens are identified on villous trophoblast.³⁸ It is suggested that, in general, MHC antigen expression "appears to be developmentally regulated and restricted to trophoblast cells outside the major maternal fetal exchange area in mature placentas."³⁸ Inducibility of Class I expression appears also to be

strictly developmentally regulated. In vitro, Class I can be induced on embryonic cells and apparently in short-term cultures of early postimplantation ectoplacental cone (EPC) trophoblast (8–9 days after conception), but not on blastocyst-derived trophoblast giant cells (5–6 days after conception).³⁸ Class I expression appears to only be inducible in villous trophoblast upon their release from the local villous milieu (i.e., in cell culture, although not in explant culture), suggesting a central role for the villous mesenchyme in controlling trophoblast Class I expression.²⁷ Despite the continuous passage of immune cells in the maternal blood stream over the syncytiotrophoblast, there is, under normal conditions, no evidence of sustained contact and suggests that the above defenses are adequate.⁷⁴ Furthermore, HLA restriction would prevent corecognition of other cell surface antigens. Notably, given the large population of uterine natural killer cells, the syncytiotrophoblast does not express natural killer target molecules.⁴⁵

Altered trophoblast expression of major histocompatibility antigens in vivo^{5, 36} has been associated with early pregnancy loss and with preeclampsia; therefore, aberrant trophoblast expression of major histocompatibility locus antigens has been proposed to lead to both fetal (HLA-DR) and maternal (HLA-G) disease. A recent animal model suggests that prevention of Class II induction on trophoblast may improve pregnancy outcome.⁸⁵ Overall, maternal immune balance, especially in maintaining a “normal” immunological bias towards T helper 2 (TH-2) responses in the uterus (as compared with TH-1), appears to be important for successful pregnancy.⁵⁸

Villous Vasculature

Early in pregnancy, villous vessels are situated deep in the villous stroma, with mean distance from intervillous space to villous vessel of 24 to 27 μm ⁷; not surprisingly, the early conceptus is relatively oxygen-poor.⁶ The placental vasculature increases in complexity, with increasing numbers of capillary outlines per villus, until about 36 weeks gestation⁸³; some placental growth continues until late in gestation.⁷³ The mature villous functional unit is a barrel, with the staves formed by the large fetal stem vessels and the villous tree arborizing toward the center where the “youngest,” or most recently formed, villi are found. The villous surface area of exchange increases throughout gestation,⁸³ and placental permeability increases even after the placental growth rate peaks by 30 to 32 weeks gestation.⁶ The microvillous surface⁸² and the proportional volume of terminal villi also increase in the third trimester. Additionally, there is a massive enlargement of the syncytiotrophoblast surface, disproportionate to syncytial volume, that may facilitate the development of vasculosyncytial membranes of the terminal villi.²⁸ In the vasculosyncytial membrane villous capillaries about the trophoblast basement membrane, with trophoblast nuclei clustering at the side. The membrane itself measures only 0.5 to 1.0 μm in thickness; the capillary and trophoblastic basal laminae may appear to fuse.¹⁰

The anatomy of the evolving villous vasculature has been well studied and has been recently summarized.²¹ Early critical events appear to parallel those in the macaque.⁴⁶ The best evidence is that as early as day 21 to 22 after conception (approximately 5 post-menstrual weeks) the first macrophage-like cells develop in the primitive secondary villous mesenchyme. At the same age, in early tertiary villi, hemangiogenic cell clusters were seen, in the centers of which intercellular clefts appeared and began to dilate, forming a primitive lumen. No endothelial basal lamina could be identified at this stage. The appearance of stromal macrophages concomitant with (or even prior to) hemangioblastic cells may suggest that macrophages play a role in the early differentiation of villous mesenchyme and may influence early vasculogenesis. By 8 weeks' gestation, some villous stromal macrophages can be demonstrated to have Fc-gamma receptors; the proportion of immunophenotypic monocyte/macrophages that also have Fc-gamma receptors increases until the mid-trimester.⁸⁰ Villous macrophage Fc-gamma receptors have long been attributed to a primary function in the clearance of maternal anti-fetal/paternal antibodies by entrapping relevant fetopaternal antigens and phagocytosing potentially deleterious immune complexes outside of the fetoplacental circulation.⁹⁰ The magnitude of potential fetal injury when the villous stroma does not adequately sieve antibodies is seen in Rhesus isoimmunization, in which case the erythrocyte-specific Rhesus antigen is not present in the villous stroma, and there is free passage of anti-Rhesus immunoglobulin into the fetal circulation.

One week later (day 29 after conception), villi without vasculogenesis were the exception. Stromal macrophages remained numerous; within putative vascular cords, endothelial cells were clearly recognized, as well as pericytes. Later, vasculogenesis may be best thought of as differing quantitatively (rather than qualitatively) from these early processes. Occluding endothelial junctions were seen by days 32 to 35 after conception, and the beginnings of a basal lamina were seen by week 6. Angiogenesis proper did not occur in the latter half of pregnancy; therefore, vascular growth occurs via mitotic activity of existing endothelial and pericytic cells, rather than by recruitment of mesenchymal precursors. Only in the last 10 weeks of pregnancy do the villous capillaries have an intact basal lamina.

Although the barrier provided by an intact basal lamina is a late phenomenon, from as early as 8 weeks, functionally active Fc-gamma receptor was detected on villous endothelial cells. All three subtypes of Fc-gamma receptor can be detected on first trimester endothelium; the number of immunoreactive vessels does increase with increasing gestational age. These receptors may bind and prompt phagocytosis of potentially deleterious immune complexes.⁸⁰ In transplacental immunoglobulin transfer c-gamma receptor function begins early as well; IgG is detectable from about 8 weeks in fetal serum.³¹ All four subclasses of IgG are transferred across the placenta, but at different relative rates at different stages of gestation. By 26 to 34 weeks, fetal levels generally are greater than maternal levels.⁸

MECHANISMS OF PLACENTAL INJURY

The fact that breach of the trophoblastic layer is routine in pregnancy is demonstrated by the common (but not universal) presence of paternal histocompatibility antigen antibodies in maternal serum. Major factors complicating placental analysis in regards to vertical transmission are the extreme regional variation within the placenta, making tissue sampling problematic, and the focal nature of most if not all placental lesions. A recent in vitro study brought this issue squarely home. Although, *overall*, the investigators found no statistically significant difference in placental permeability in cases with elevated maternal serum alpha-fetoprotein compared with normal maternal serum alpha-fetoprotein, two of the nine placental units in the group with elevated alpha-fetoprotein (and therefore overall increased placental permeability) had permeability greater than 5 standard deviations above the mean for all other cotyledons. The obvious explanation for this finding of *focal* changes in placental permeability (and integrity of the placental barrier) is *focal* placental lesions, which are the rule, rather than the exception.¹⁶

The most common mechanisms of placental injury are (1) uteroplacental vascular pathology, with villous injury secondary to malperfusion or nutrient deprivation; (2) intraplacental vascular injury, often occurring secondary to extrinsic (uteroplacental) malperfusion, but also associated with chronic inflammation and pathologic coagulation; (3) chronic inflammatory lesions, either reflecting congenital viral infection or maternal/fetoplacental immune pathology; or (4) coagulation associated injury, which may be associated with either utero- or fetoplacental malperfusion, or seen as a primary coagulopathy.

Uteroplacental Malperfusion

Physiological change of the spiral arteries describes their appearance after the original musculo-elastic tunica media is replaced by mononuclear trophoblast embedded in fibrinoid.¹³ Physiologically changed arteries form a high capacitance circulation that is insensitive to vasoactive stimuli, protecting the fetus from undesirable fluctuations in maternal blood supply. The most outstanding uteroplacental vascular lesion is the complete or partial absence of physiological conversion of spiral arteries (documented most extensively in preeclampsia).¹⁴ Interstitial invasion in preeclampsia is unrestricted; the invasive defect appears to be selective for trophoblast endovascular invasion. Because unconverted vessels retain high resistance or low capacitance properties, the effect on maternal blood supply to the placenta may be dramatic. Doppler and isotope studies in the human suggest that uteroplacental flow is decreased to 50% to 70% of normal.^{51, 84} Nonconverted vessels may be prone to atherotic lesions, characterized by fibrinoid necrosis, infiltrating leukocytes and macrophages, and lipid-containing foam cells.⁶² Pathologic uteroplacental thrombosis is not uncommon in preeclampsia and compli-

cated pregnancies with uteroplacental vascular pathology (including the phospholipid antibody syndrome).⁷⁸

When uteroplacental vascular lesions are present, the resultant disturbance in resistance, capacitance, and increased fragility of the vasculature predisposes to "uteroplacental vascular accidents" such as placental infarcts¹⁵ or abruption,²³ both of which damage the trophoblast barrier, villous stroma, and fetoplacental vasculature and may have implications for vertical transmission. Abruptio is a hemorrhagic uteroplacental vascular accident, whereas an infarct is an ischemic vascular accident. In abruption, the placenta is forcibly detached from the uterine wall by retroplacental hemorrhage.⁸⁹ Such placental trauma may cause placental "bruising," seen as villous stromal hemorrhages that may be a precursor lesion to frank fetomaternal hemorrhage. By contrast, placental infarct develops following a uteroplacental vascular occlusion without vascular rupture, with cessation of intervillous flow ceases, and collapse of the intervillous space and villous necrosis. Chronically abnormal uteroplacental vascular perfusion may more diffusely impair the growth and development of the placenta. Scarred, shrunken, fibrotic, and hypovascular villi, with reduced number or caliber of placental capillaries, have been proposed to result from destruction of growing villous capillaries by abnormal uteroplacental flow.³⁰ Such capillary damage may lead to fetomaternal hemorrhage. Watson et al⁸⁶ have developed a model of the villous stromal response to injury, at least in the first trimester, and have found pronounced expression of TGF- β , heavy infiltration by villous stromal macrophages, and late deposition of tenascin as integral components of villous healing activity. Macrophage recruitment following villous wounding may be relevant to vertical HIV transmission because these cells may not only be important cellular reservoirs of the virus but also may produce a variety of other inflammatory mediators that may influence immune status and affect transmissivity. Because a phenotypic maturation of the villous macrophage can be clearly demonstrated across gestation,³² it is also tempting to speculate that the same maternal immune environment may elicit different villous macrophage responses—and potentially different fetal effects.

Intraplacental Vascular Lesions

Chronically abnormal uteroplacental vascular perfusion can lead to intraplacental vascular lesions, either due to chronic nutrient deprivation (and failure of growth), or as a result of abnormally high pressure⁴⁴ or abnormally turbulent intervillous flow (damaging developing tissues).⁴⁴ Histologically, the villi are scarred, shrunken, fibrotic, and hypovascular, with both reduced number and diminished caliber of placental capillaries. Other abnormalities of the fetoplacental vasculature, which are common in association with uteroplacental vascular lesions (and abnormal umbilical arterial Doppler velocimetry) include (1) mural or occlusive fibrin thrombi in chorionic and fetal stem vessels, (2) avascular terminal

villi, (3) "hemorrhagic endovasculitis,"⁸¹ (4) reduction or obliteration of chorionic or fetal stem vessels by mural hyperplasia (identified by a decreased/absent lumen area and increased wall thickness), (5) mural disorganization (diagnosed when the normal concentric organization of the arterial wall was interrupted over at least 50% of its circumference), and (6) abnormally thin walled arteries (diagnosed as such when all structures in a large or small fetal stem vessel were histologically similar, implying that the obligatory artery in the fetal stem had vein-like characteristics). The latter two lesions are believed to represent remodeling effects of aberrant blood flow within the local fetoplacental vasculature.

Chronic villitis/intervillositis may also be associated with intraplacental vascular damage or dysfunction. Chronic intravillous inflammation (villitis) may be frankly destructive, activating endothelium and promoting vaso-obliteration or by the initiation of a frank destructive vasculitis. Inflammatory cytokines and other signals produced by chronic perivillous inflammation (intervillositis) may also indirectly affect placental vasomotor function (possibly via the stromal macrophage as an intermediary).

Hemorrhagic endovasculitis (HEV) may be the villous vascular barrier lesion par excellence. Histologically, it appears to be characterized by early endothelial injury or loss. Shen-Schwartz⁷⁷ suggested that HEV is the result of local circulatory instability. As such, it not surprising that HEV is very common in cases with absent or reversed umbilical arterial flow.⁷¹ HEV is common in the vicinity of infarcts, near degenerating chorangiomas, in areas of shared circulation in cases of twin transfusion syndrome (in which bi-directional flow may occur), and in foci of chronic villitis. As a tissue marker of the presence and extent of placental (and by extension, fetal) circulatory destabilization, HEV may be relevant to considerations of impaired placental barrier function.

Abnormally proliferative placental vascular development is commonly related to maternal diseases involving overgrowth of the placenta as a whole, cardinal among these being maternal diabetes mellitus.⁶⁸ Vascular proliferation may be seen in other conditions, including fetal growth restriction³ and twin gestations, in which case two fetuses are competing for a single volume of uterine blood flow. Such capillary proliferation may be an endothelial response to decreased oxygen availability.³ The possible role of placental macrophages in the regulation of villous connective tissue and vasculature outgrowth has been widely speculated^{18, 21} and also inflammatory cytokines are recognized mediators of angiogenesis.

Inflammation-Associated Lesions

Acute Inflammation

In the vast majority of cases, processes of acute inflammation will affect the amniotic fluid compartment, in the forms of acute ascending

or intraamniotic infection. For additional information, refer to the comprehensive review of Schmidt.⁷⁵ The human amnion forms at the end of the first week of conception as an expanding space filling with fluid between the cells of the embryoblast and the trophoblast. The primitive amnion epithelium differentiates from the embryonic ectoderm, and the amnion connective tissue forms from the layer of the extraembryonic mesenchyme. The yolk sac is a resorptive organ with an extensive microvillus surface; the predominant transport mechanism is likely exocytosis. Different subpopulations of amnion epithelial cells can be identified by electron microscopy; the amnion surface may be best considered as a mosaic of cells with either secretory or absorbent characteristics. At term, the microvilli are often focally absent, possibly due to cell injury. Focal or extensive amnion cell death and denudation of the basal lamina is common at delivery. The umbilical epithelium is similarly organized so that from a morphological standpoint, all prerequisites for transepithelial transport are present. Collagen is laid down by the fibroblasts of the amnion and chorion; specific histiocytes have differentiated by the 10 mm stage, either forming *in situ* before the amnion and chorion fuse, or migrating from the chorion. These cells are capable of phagocytosis and may contribute to clearance of some substances (e.g., meconium), but no known role in transport has been identified. Among the chorionic cytotrophoblasts, two types can be identified, one of which appears to be specialized for endocytosis, and a second vacuolated cell that may function in storage. Following the formation of the chorion laeve, the role of chorion cytotrophoblasts may be more of a diffusion barrier, rather than in active transplacental transfer. The junctional zone at which there is actual fetal or maternal contact is an area in which most of the cells are nonvital. Often, a large component of this junction is degenerate material, derived either from chorionic cytotrophoblast, decidua, or both. The observation that wandering lymphocytes tend to stop here has led to the speculation that this material is likely an "integral component of the immune barrier."⁷⁵

An ascending organism may either colonize the extraplacental membranes or cross membranes (intact or ruptured) into the amniotic fluid. If there is decidual or choriodecidual *infection*, neutrophils are recruited out of the decidual capillary bed by locally generated cytokines, but they remain within the decidua. This (often focal) decidual inflammation and necrosis has been termed *necrotizing deciduitis*.⁶⁵ If, on the other hand, bacteria or their toxins gain access to the amniotic fluid without choriodecidual colonization distant from the site of rupture, neutrophil chemotaxis is instead directed toward the amnion (margination).⁶⁵ The types of questions that can, more or less routinely, be answered by placental examination include: Did bacteria ascend across the cervix? Did bacteria gain access to the amniotic fluid space? Was there a generalized intraamniotic infection, and (within limits) for how long was it present? Did the fetus respond to the infectious process? This last question may be relevant if immune activation alters HIV transmissivity. A fetal response to intraamniotic infection is shown by marginating fetal

leukocytes in umbilical cord and chorionic vessels; fetal inflammatory response is a better predictor of a positive amniotic fluid culture than maternal inflammation in chorion, decidua, and chorionic plate.⁶⁵ If the mother is immunoincompetent (e.g., excluding maternal HIV infections), the fetal inflammatory response will be disproportionately greater than expected for the level of maternal inflammation. The same finding (of disproportion between fetal and maternal inflammatory responses) may accompany catastrophic fetal streptococcal sepsis.

In the broadest terms, the histologic progress of acute intraamniotic infection involves increasing numbers of recruited neutrophils and increasing distance traveled from their site of origin. As in any other tissue in the body, these two features depend upon the size of bacterial inoculum, the immunogenicity of the agent, the host's ability to respond to the agent, and the duration of exposure to the infectious stimulus. Attempts to isolate the *timing of onset* of infection may be fraught with peril because turnover of cytokines in the amniotic fluid compartment (a space lined by amnion and chorion that lacks lymphatics or capillaries) appears to be slow.⁷² Neutrophil karyorrhexis may indicate a relatively longer duration of intraamniotic infection; similarly, combination patterns—of nuclear dust and fresh neutrophils—may be correlated with clinical evidence of reinfection or superinfection.

Amniotic fluid infections may alter composition of the amniotic fluid, as well as the structural integrity of the extraplacental membrane barriers. The mature amniotic fluid compartment permits two potential paths of transport: (1) placental exchange (maternal blood across placental barrier, to fetal blood and vice versa), and (2) paraplacental exchange (maternal blood of decidual vessels to fetal membranes to amniotic fluid, to skin or gastrointestinal tract, to fetus and reverse).

Transepithelial fluid transport may occur throughout pregnancy; amnion epithelium may appear to have active apocrine secretory function. Macrophages have been reported by Hoyes (1968) to be present in the amniotic fluid by the fifth month; they later disappear. The main role of transmembranous fluid exchange may be as a "valve" to take care of whatever the fetus does not manage via gastrointestinal and pulmonary secretory or resorptive routes. The role of cytokines and other inflammatory mediators, not to mention the direct effects of microorganisms on the complex functions of the extraplacental membranes, both as barrier and as transport surface, should not be underestimated. Clinically, that some disruption of normal membrane function may be present is suggested by the association of oligohydramnios with acute intraamniotic infections, both preterm and at term.^{60, 64}

Chronic Inflammation

A few decidual lymphocytes are normally present in the decidua of the basal plate and the extraplacental membranes. One component of the normal decidual leukocyte population, the large granular lymphocytes, may contribute to the limitation of trophoblastic penetration of

maternal tissues.⁸⁸ In uncomplicated term pregnancies, clustering of maternal lymphocytes near anchoring villi, and even sparse infiltration—with preservation of the anchoring villous structure—are common. Chronic destructive anchoring villitis is more common, in our experience in complicated gestations, especially in the context of fetal growth restriction or maternal preeclampsia. The inciting stimulus is unknown, but this lesion is more common in patients with poor reproductive outcome.⁴⁸

Chronic choriodecidualitis/amnionitis indicates not only a denser distribution of decidual lymphocytes than expected but also the migration of (maternal) decidual lymphocytes into the (fetal) chorion or amnion. Although this has been associated with chronic bacterial infection (such as syphilis), it is more commonly seen in patients with no history of, nor risk factors for, sexually transmitted diseases. Like other chronic inflammatory lesions, it is most likely an auto- or alloimmune response of maternal lymphocytes to trophoblast or placental stromal antigens.⁴⁷ In the basal plate, dense chronic decidual inflammation or plasma cell infiltrates and chronic uteroplacental vasculitis are common in complicated pregnancies.⁶⁹

The differential diagnosis of chronic villitis is generally considered to include both congenital viral infection and maternal/fetal allograft-type "rejection" reactions.^{49, 66} Specific patterns of inflammatory pathology that may be correlated more with specific infectious agents, including *T. pallidum*, *L. monocytogenes*, *T. gondii*, cytomegalovirus, and rubella are summarized by Gersell.²⁹ Chronic villitis is seen in cases of recurrent pregnancy failure in the absence of evidence of recurring infection⁶⁷ and may be a common finding in patients with both clinical autoimmune disease and subclinical (e.g., serologic) evidence of autoimmunity. Antiphospholipid antibodies have been demonstrated to be cross-reactive with trophoblast phospholipids in chronic villitis³⁷; the focal lymphocyte recruitment may be initiated by immune complex formation and immune-mediated cell injury. The implications of chronic villitis for future pregnancies depends upon intercurrent maternal disease and past pregnancy outcome.

Chronic villitis is diagnosed by the presence of lymphocytic villous stromal infiltrates; the infiltrate may include lymphocytes, monocyte/macrophages, plasma cells, and, rarely, eosinophils, with macrophages and T lymphocytes usually predominant.^{2, 34} The majority of intravillous inflammatory cells may be maternal in origin.⁵⁹ Chronic villitis is commonly associated with syncytial loss and perivillous fibrin deposition, chronic fetoplacental vasculitis and intraplacental vascular obliteration.⁷⁰ Chronic intervillitis has also been observed in recurrent pregnancy loss.²⁴ Like chronic villitis, it may represent a maternal response to placental alloantigens or to autoantigens common to mother and placenta.⁴⁹ It is almost always seen with chronic villitis at term but is more commonly an isolated finding in preterm placentas. In chronic intervillitis, many of the intervillous cells are reactive immunohisto-

chemically for IgM, IgG or IgA, which may indicate intervillous immune complexes.

Coagulation-Associated Lesions

The potential targets for pathologic coagulation include the (maternal) uteroplacental vasculature, the basal plate (including Nitabuch's fibrin), the intervillous space, the villous (syncytiotrophoblast) surface, and the fetoplacental vasculature.

Fibrin/fibrinoid deposition in the basal plate has been proposed to be a by-product of maternal-placental immunologic interactions; increased basal plate coagulation has been identified in cases of pregnancy compromise believed to be of immunologic origin.⁵⁰ Increased basal coagulation results in a thick band of basal plate fibrin/fibrinoid replacing the normal zone of extravillous cytotrophoblasts and may even extend to involve several layers of entrapped and necrotic basal villi. Chronic anchoring villitis can often be seen in the "surviving" villi, perched atop the pile of necrotic and fibrinoid material. As in the extraplacental membranes, this material may contribute to the "immune barrier," but may not be the barrier to maternal lymphocytes it appears to be at the extraplacental choriodecidual interface.

Excessive perivillous fibrin or fibrinoid deposition may be considered to be a generic response to any type of syncytial injury. Any breach of syncytial integrity results in, by definition, exposure of the villous stromal to the maternal circulation. The "company kept" by syncytial injury (i.e., the concurrence of chronic uteroplacental malperfusion or chronic villitis) can help place this lesion in its proper context. Coagulation on the placental trophoblast surface may be initiated by a variety of stimuli, including trophoblast apoptosis⁵⁶ and circulating endotoxin and may play a critical role in syncytial repair.

Damage to the fetoplacental vasculature commonly results in the initiation of coagulation. Thrombotic lesions occurring in the absence of other placental lesions most commonly involve the chorionic or large fetal stem vessels and may be due to mechanical trauma to the chorionic plate vessels (such as fetal kicking of the chorionic plate or in vasa previa and velamentous vessels). Placental intravascular lesions most commonly accompany other evidence of processes that damage endothelia, such as chronic villitis. Fetal stem vessel thrombi are more commonly associated with chronic than acute inflammation. Thrombosis of large fetal stem vessels in the placenta results in downstream vascular obliteration and fibrotic, avascular villi.

CONCLUSION

Normal placental function as barrier and transporter is intimately allied with its capacity to restrict or permit vertical transmission of

infectious agents. In the implantation site, decidual resident cells, recruited monocyte macrophages, natural killer cells, lymphocytes, and placental trophoblasts coordinate a complex harmony of trophic and suppressive cytokine stimuli that not only support the well being of the conceptus but also may facilitate or block viral replication or transmission. The villous parenchyma, especially the stromal macrophage (Hofbauer cell) and the villous (endothelium) progressively acquire capacity to both transport and sieve maternal immunoglobulin and to produce and respond to cytokines themselves. The normal biology of the placenta makes the likelihood of focal/confined and transient failures of barrier function almost universal in gestation. Such breaches are commonly the effects of uteroplacental or fetoplacental malperfusion, chronic or acute inflammatory injury, or coagulation-associated pathology.

It is also common that these pathologies occur in combination. Different mechanisms of injury acting focally within the placenta, at different gestational ages and indifferent combinations with other placental lesions may explain the complex and obscure basis for vertical transmission of HIV.

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