INTRODUCTION

In order to evaluate placentas for clinically significant abnormalities, pathologists need to have a thorough understanding of the basic anatomy, how it changes during development, and how it translates into organ function. Many of the concepts of structure-function and development in the placenta have undergone dramatic change over the past several years because of advances in developmental biology and antenatal monitoring. This chapter presents the basic gross and microscopic anatomy of the placenta, highlighting artifacts and normal variants that may be confused with pathologic lesions. Briefly discussed are the overlapping development sequences that act in concert to assemble a normal term placenta, placing them in temporal context and emphasizing their clinical relevance. Finally, the basic structure-function relationships that govern the maternal and fetal circulations, the onset and timing of labor, and the maternal physiologic accommodation to pregnancy are considered.

GROSS AND MICROSCOPIC ANATOMY

Amnion and Membranous Chorion

The amnion is a simple squamous epithelium with an underlying basement membrane and an associated band of loose connective tissue approximately 5 to 10 cells in thickness (fig. 1-1). It forms the inner lining of the amniotic cavity, covering the chorionic plate and its extension in the fetal membranes, the chorion laeve. An attenuated layer of amniotic epithelial cells also surrounds the umbilical cord. Amnion represents the extraembryonic extension of fetal skin, with which it shares a number of characteristics including pemphigoid antigens and cytokeratins (69). At areas of repetitive stress, such as at the umbilical cord insertion, amnion may undergo metaplasia to form plaques of keratinizing, stratified squamous epithelium, 0.5 to 2.0 cm in diameter, which may be seen by gross examination (see chapter 7, Squamous Metaplasia).

Amnion is easily separated from the underlying chorion in both membranes and chorionic

Figure 1-1

PLACENTAL MEMBRANES

The amnion (top) consists of simple cuboidal epithelium with a thin layer of underlying fibroblasts; it is separated from the underlying chorion by a narrow space. The chorion is composed of connective tissue with a subjacent band of eosinophilic, mononuclear trophoblast which contains a few hyalinized villi. Underlying the chorion is the maternal decidua, consisting of decidua capsularis and decidua vera from the opposite side of the uterus. A cleft-like space marks the point of fusion (arrow).
Plate, and once separated, is easily torn. Isolated tears in the amnion frequently occur during labor and delivery or at the time of placental examination, but infrequently prior to labor. It is important not to misinterpret shreds of torn amnion hanging off the umbilical cord as pathologic amnionic bands (see chapter 7, Amnionic Bands). The yolk sac, a vestigial organ in human pregnancies, may be seen immediately beneath the amnion as either a yellow plaque at the time of gross examination (fig. 1-2) or a calcified nodule at microscopic examination (fig. 1-3).

The membranous chorion (chorion laevae) is formed by the collapse of the placental intervillous space during membrane development (see below). It is composed of a heterogeneous mixture of mononuclear trophoblastic cells, with either vacuolated or eosinophilic cytoplasm, plus a few widely scattered atrophic chorionic villi. Below the chorion laeaeae trophoblast is decidualized maternal endometrium; above is a layer of avascular connective tissue. The connective tissue of the chorion and amnion is distinct and held together by thin fibrils of

Figure 1-2

**YOLK SAC**

A pale yellow plaque lies between the chorionic plate and the overlying amnionic epithelium (below center).

Figure 1-3

**YOLK SAC**

The yolk sac degenerates in late pregnancy to form a calcific plaque below the amnion.
collagen. Recent data suggest that a fetal genetic polymorphism may lead to overexpression of a membrane collagenase in some patients with premature membrane rupture (29).

**Umbilical Cord**

The umbilical cord is the cable linking the fetus to the placenta (fig. 1-4). Within the cable are two muscularized arteries and a single, large, thin-walled vein embedded in a hydrated extracellular matrix gel known as Wharton's jelly. The cable is usually twisted to some degree, generally to the left (i.e., the diagonal twists run from upper left to lower right), with an average of 2.1 twists per 10 cm at term (76). On cut section, the paired arteries are distinguished from the vein by thicker walls and a smaller lumen. The thicker wall of the artery is composed of a tightly bundled outer circular layer of smooth muscle and an inner spiral longitudinal layer, which contracts to occlude the placental circulation at the time of delivery (folds of Hoboken) (71). An anastomosis between the two arteries (Hyrtyl's anastomosis) near their decussation at the chorionic plate acts to balance the two circulations and obviates any adverse consequences following involution or failure to develop of one of the two arteries (see chapter 8, Single Umbilical Artery) (64). The umbilical vein may be focally ectatic, forming varicosities that have been termed false knots. These varicosities are of no clinical significance.

![Figure 1-4](image1.png)

**UMBILICAL CORD**
The thin-walled vein is seen on the left and the two thick-walled arteries on the right. The vessels are surrounded by a hypocellular matrix gel known as Wharton's jelly. The inner circular layer of smooth muscle, which contracts to obstruct arterial flow at parturition, is best seen in the artery on the lower right.

![Figure 1-5](image2.png)

**ALLANTOIC DUCT REMNANT**
The allantoic duct lies between the two umbilical arteries which follow its course from the fetus to the chorionic plate. It arises from the roof of the bladder and is lined by transitional epithelium. In some species the allantoic sac plays an important role in fetal nutrition, but it is vestigial in man.

Two additional structures in the early umbilical cord, which may persist into the second and third trimesters, are the transitional epithelial-lined allantoic duct (fig. 1-5), lying directly between the two arteries, and the intestinal epithelial-lined vitelline duct (fig. 1-6), with or without its accompanying omphalomesenteric arteries (see chapter 8, Vestigial Remnants). The vitelline duct and its vessels communicate with the yolk sac in early pregnancy. The umbilical
cord insertion is generally near the center of the placental disc (fig. 1-7), but may be displaced to any location on the chorionic plate or in the membranes because of asymmetry in the process of membrane formation (described below). The vessels within the umbilical cord that insert in the membranes may become occluded by torsion during gestation or torn at the time of membrane rupture, leading to fetal hemorrhage (see chapter 8, Insertion Anomalies).

Chorionic Plate and Stem Villi

The chorionic plate (fetal surface of the placenta) is normally covered by a layer of glistening amnion. Chorionic arteries and veins branch from the umbilical cord insertion. Arteries pass over veins. Plaques of yellow-white subchorionic fibrin bulge slightly upward. The normal color ranges from gray-blue to red. Membranes normally arise from the margin of the round-oval disc.
branch from the umbilical vessels and extend in every direction, stopping at the peripheral margin of the placental disc; arteries travel over veins. Approximately 40 major primary stem villi, each measuring 0.5 to 1.5 mm in diameter, protrude perpendicularly downward from the chorionic plate (10). These in turn each separate into 4 to 8 secondary stem villi, which travel parallel to the chorionic plate.

Microscopically, the chorionic plate and stem villi, both primary and secondary, are composed of dense collagenized connective tissue surrounding thick-walled arteries and veins (fig. 1-8). It is difficult to distinguish whether any given vessel is an artery or vein, but veins generally have thinner walls than arteries. The trophoblast that originally surrounds stem villi is largely replaced by fibrin, which deposits as a consequence of vascular stasis. Since this fibrin is surrounding non-gas exchanging structures it has no clinical significance.

The more distal extensions of major stem villi include immature intermediate (anchoring) villi, which implant in the basal plate (see below), and mature intermediate (tertiary stem) villi, which develop early in the third trimester (16). Mature intermediate villi give rise to terminal villous units (discussed below). At the end of this process, each primary stem villus in the mature placenta has given rise to approximately 10 to 15 total branching generations of smaller villi (45). A more rigorous discussion of the process of villous morphogenesis, with illustrations, can be found elsewhere (4). At term, major stem villi may show remnants of a peripheral paravascular capillary net, more typical of earlier stem villi (fig. 1-9). This subtrophoblastic capillary net can proliferate to form chorangiomas or diffuse chorangiomatosis (see chapter 4) (61).

**Terminal Villous Unit and Interhemal Membrane**

The terminal villous unit consists of the most distal portion of the mature intermediate stem villus that contains a muscularized arteriole plus the terminal villi arising from it (fig. 1-10) (81). At this point, flow into gas exchanging villi is regulated by placental arteriolar tone. The terminal villi are composed of capillaries, fetal macrophages (Hofbauer cells), and a few perivascular fibroblasts without associated collagen.

The surrounding trophoblast bilayer is stretched thin, so that only the outer syncytiotrophoblast layer is seen in most villi. Normal terminal villi contain one or more attenuated regions where capillaries are intimately applied to the trophoblast basement membrane. These regions, known as vasculosyncytial membranes, constitute the interhemal membrane, where the majority of gas exchange occurs (42). Focal aggregates of degenerating syncytiotrophoblast nuclei (syncytial knots), especially prominent in placentas with
evidence of maternal underperfusion, are seen in most term placentas. They may have adaptive significance by attenuating the cytoplasm of adjacent trophoblast, decreasing the thickness of the interhemal membrane, and maximizing gas exchange (80). The growth of terminal villi is driven by capillary proliferation (angiogenesis) (43). Imbalances between capillary and adjacent stromal growth can lead to hypercapillarization (see chapter 4, Villous Chorangiosis), another placental adaptation that may enhance gas exchange.

**Basal Plate and Anchoring Villi**

The basal plate (maternal surface) is dark red, with a smooth to pebbled texture attributable to sheets of extracellular matrix material corresponding to the so-called stria of Rohr and Nitabuch seen on microscopic examination (fig. 1-11). The surface of the basal plate and the immediately adjacent intervillous space often undergo variable amounts of calcification, which has no clinical significance. The contour of the basal plate is coarsely folded, forming clefts...
known as placental septa that protrude into the parenchyma and can extend as far as the fetal surface. Septa form as a consequence of continuing radial placental growth after fixation of the membrane margin (sealing of the closure ring) and have no functional significance. Entrapped nests of basal plate trophoblast in the septa can secrete clear fluid to form septal cysts, which are of no clinical significance (figs. 1-12, 1-13).

Microscopically, the basal plate contains a variety of elements (fig. 1-14). Anchoring villi, the most distal extensions of the primary stem villi, insert in and are often surrounded by maternal endometrium. The trophoblast cells lining the endometrial aspect of the anchoring villi differentiate to form invasive intermediate trophoblast (fig. 1-15) (7,24). This intermediate trophoblast synthesizes copious amounts of
extracellular matrix material, particularly enriched in a specific molecule known as oncofetal fibronectin, which accumulates between the trophoblast and the underlying endometrium (stria of Nitabuch) (27). Trophoblastic giant cells (placental site giant cells) form when the intermediate trophoblast achieves its maximum extent of invasion (fig. 1-16). Since this usually occurs within the myometrium, the finding of excessive giant cells in the basal plate may be an indication of abnormally superficial implantation. Occasionally, dilated maternal arteries lined by fibrinoid matrix and scattered endovascular trophoblast may be seen (see below). Maternal veins generally run parallel to the basal plate and are less conspicuous. These veins may also contain variable amounts of trophoblast and fibrinoid, particularly on the side facing the placenta (6,20).

A background population of mononuclear cells in the attached decidualized endometrium is common. Plasma cells are not normal in this location. Fragmentation of the maternal surface of the placenta (basal plate) may be associated with retained placenta and should be communicated to the clinician. The absence of an endometrial layer between the trophoblast and smooth muscle in the basal plate is indicative of placenta accreta (see chapter 4), while the presence of a few smooth muscle fibers within decidualized endometrium is not.

**Placental Margin and Membranes**

The placental margin is normally characterized by a sharply demarcated transition between the placental disc and the attached membranes. In some cases this transition zone may be less abrupt, or even markedly irregular, and the placenta may assume various nondiscoid shapes (see chapter 4, Disorders of Placental Migration). The transition zone is characterized histologically by the collapse of the intervillus space,
leaving only a few atrophic villi and a band of trophoblast sandwiched between the fetal surface (fibrous chorion and amnion) and the maternal surface (decidualized endometrium with maternal blood vessels).

Formation of the placental margin is somewhat more complicated than simple atrophy. Since the gestational sac forms on one side of the uterus and eventually fuses with the opposite wall, it is clear that the margin must actually represent a fold, composed of the endometrium covering the implanting gestational sac and that of the opposite uterine wall. This fold creates a potential space where blood can accumulate, leading to the circumvallate placenta (see chapter 4). It has become apparent that the placenta grows laterally during early gestation by a process of villous attachment to and extension into large lateral uterine veins (discussed in more detail below) (22,59). This leads to the formation of a dilated marginal venous sinus which drains a substantial amount of the blood in the intervillous space (fig. 1-17). Transient increases in maternal venous pressure may lead to rupture of these engorged marginal veins (fig. 1-18) (33,67).

DEVELOPMENTAL ANATOMY

The purpose of this section is to simplify the complex subject of placental development by separating it into compartments, and considering processes and events in terms of when they occur relative to the last menstrual period (10,25,)
Further details regarding the developmental biology of human and rodent placental development can be found in recent reviews (23,35).

**Blastocyst Trophoderm (Days 18 to 20 of Menstrual Cycle)**

A morphologically evident trophoblast first becomes distinct from the embryonic inner cell mass at the 16-cell stage of development, prior to implantation. Experimental work in animals implicates a specific array of growth factors secreted by the embryonic inner cell mass that maintain the pluripotency of these trophoblast stem cells prior to contact with the maternal endometrium (77).

**Nidation and Maternal Capillary Circulation (Days 20 to 28 of Menstrual Cycle)**

Nidation, or apposition, refers to the binding of the blastocyst trophoderm to the endometrial epithelium, a process that involves a number of growth factors, adhesion molecules, and cytokines (14). Within days of nidation, the blastocyst translocates across the epithelium to lodge in the endometrial stroma directly adjacent to one of the approximately 4,000 spiral arteries in the uterus. The placenta at this stage is referred to as a primitive trophoblast plaque. The trophoblast proliferates and differentiates to form a primitive syncytiotrophoblast, which erodes adjacent capillaries and venules to form intracellular lacunae (fig. 1-19). These lacunae eventually enlarge and become remodeled to form the definitive intervillous space. Columns of primitive syncytiotrophoblast, lying between the enlarging lacunar spaces, are invaded by cords of cytotrophoblastic cells which grow down from the primitive chorion to form “primary villi.” It seems likely that the remnants of the primitive syncytiotrophoblast disappear or are overgrown by the mature syncytiotrophoblast, which forms by fusion and terminal differentiation of the invading cytotrophoblast (see below).

**Chorionic Plate and Body Stalk (4 to 5 Weeks from Last Menstrual Period [LMP])**

Mesoderm derived from the inner cell mass grows out from the allantois through the body stalk to form a sheet covering the primitive chorion. In rodents, fusion with the chorion depends on specific molecular interactions between the allantoic mesoderm and the trophoblast (31).

**Villous Stromal Vasculogenesis (5 to 6 Weeks from LMP)**

Vascuogenous villous stroma develops from extraembryonic mesoderm derived from the degenerating hypoblast of the primitive yolk sac (5). Downgrowth of this stroma into the recently formed primary villi forms “secondary villi” (fig. 1-20). Capillaries develop in situ from this extraembryonic mesoderm following induction by the adjacent trophoblast (fig. 1-21).
The formation of villous capillaries transforms secondary villi into primitive “tertiary villi” (fig. 1-22). The villous capillary network forms in parallel with, and independent of, the paired umbilical arteries that emanate from the iliac arteries along the allantois and the formation of a beating heart in the embryo. Anastomosis of capillaries with larger vessels in the placenta at about 6 weeks is contemporaneous with the same process in the central nervous system. Development of other organ vascular beds follows shortly thereafter. A practical implication of parallel development of capillaries and larger vessels is that capillaries may be seen within villi and below the chorion in gestations without a viable fetus, such as hydatidiform moles or other anembryonic pregnancies (44).

**Elaboration of Mesenchymal Villi** *(6 to 8.5 Weeks from LMP)*

The transition from unbranched, primitive tertiary villi to the finger-like mesenchymal villi seen most commonly in early elective terminations occurs through iterative cycles...
Prior to 10 weeks’ gestation, chorionic villi branch as finger-like mesenchymal villi with abundant loose connective tissue stroma. From their origin in the chorionic plate to their terminal branches, the villi are uniform in appearance.

Early mesenchymal villi are characterized by scant connective tissue and an absence of thick-walled fetal vessels. These features help the pathologist separate early to mid-first trimester placentas from later stages.

**Development of Stem Villi**

**(8.5 to 11.5 Weeks from LMP)**

Immature intermediate villi, characterized by more densely collagenized connective tissue stroma and thicker-walled fetal vessels, are formed in the late first trimester. They provide the enlarging placenta with greater structural support for the higher pressure circulation required to perfuse the enlarging villous tree (fig. 1-24).

**Early Implantation and Arterial Plugs**

**(6 to 12 Weeks from LMP)**

Early implantation is mediated by trophoblast derived from that portion of the anchoring villus in direct contact with maternal endometrium at the floor of the intervillous space. This trophoblast first proliferates to form a confluent sheet known as the cytotrophoblast shell at the floor of the placenta. Some trophoblast in the shell then undergoes an epithelial-mesenchymal transformation to form invasive intermediate trophoblast, which permeates the endometrium in the vicinity of the placenta (implantation site) (fig. 1-25).
After 10 weeks, as the placenta enlarges, villi near the chorionic plate acquire thick-walled vessels and a sheath of more cellular fibroblastic connective tissue.

A fascinating and still somewhat controversial aspect of placental development is that despite early invasion of the uterine arteries, arterial circulation to the intervillous space is not fully established until 10 to 12 weeks of gestation (15,39). Prior to this time, endovascular trophoblast derived from the cytotrophoblast shell adopts a pseudovasculogenic phenotype and grows down into the arterial lumens, forming loose cellular plugs which act as sieves to restrict arterial flow to the intervillous space (fig. 1-26) (86). Some believe that most of the circulation to the intervillous space at this stage is indirect, depending on anastomoses connecting capillaries and veins with arteries distant from the implanting placenta. Two hypotheses have been advanced for this peculiar developmental sequence: first, that the poorly supported, early intervillous space might be obliterated by the pressure associated with a direct maternal arterial circulation and second, that oxygen-free radicals generated at the oxygen tension of arterial blood are toxic to the developing trophoblast (40). The functional consequence of indirect perfusion is that many developmental sequences in the early placenta take place in an anaerobic environment. Some early abortions associated with marked intervillous hemorrhage may be the result of premature arterial perfusion of the intervillous space.
Figure 1-26
CYTOTROPHOBLAST PLUG IN SPIRAL ARTERY
Mononuclear endovascular trophoblast cells from the cytotrophoblast shell grow down the lumens of spiral arteries to form loose plugs which retard arterial blood flow to the intervillous space.

Late Implantation and Arterial Remodeling
(12 to 20 Weeks from LMP)
Implantation by the intermediate trophoblast has traditionally been separated into two distinct phases: primary, which is confined to the endometrium as described above and secondary, which involves extension of the trophoblast into the inner third of the myometrium (fig. 1-27) (63). Concurrent with secondary implantation, the endovascular trophoblast filling the lumens of uterine arteries invades the muscular wall, leading to dissolution of the muscular media and fixed vascular dilatation. This process creates a low pressure arterial circulation protected from vasospastic influences (figs. 1-28, 1-29). This trophoblast-dependent remodeling is supplemented by trophoblast-independent vascular remodeling, which has been shown in rodents to depend on cytokines secreted by uterine natural killer cells (2,21). Recent publications have deemphasized the separation of primary and secondary phases of implantation and consider the entire process of implantation as a continuum carefully regulated by factors such as ambient oxygen tension, growth factors, and cytokines (12,13,70,73). Deficient implantation and inadequate arterial remodeling predispose to the clinical disorder known as preeclampsia (see chapter 4, Distal Villous Hypoplasia with Placental Undergrowth and chapter 6, Decidual Vasculopathy).

Figure 1-27
SECONDARY IMPLANTATION
Invasive intermediate trophoblast permeates the myometrium. Trophoblast cells at this location are spindle shaped with hyperchromatic nuclei.
Anatomy, Structure, Development, and Function

Membrane Formation and Peripheral Expansion (9 to 18 Weeks from LMP)

The formation of the placental membranes converts the placenta from a sphere protruding from one uterine wall to a disc surrounded by a thin sac that fills the uterine cavity. This process occurs in several stages. First, at about 9 to 11 weeks, the previously free amnionic sac fuses with the chorionic connective tissue, coincident with atrophy of the intervillous space at the periphery of the placenta. As the placenta grows and the sac enlarges, the remnants of intervillous trophoblast condense to form the chorion laevae, a layer that provides structural integrity for the adjacent and poorly supported fetal amnion and maternal decidua.

Recent data have shown that in addition to interstitial growth by elaboration of villous trees, the placenta also grows laterally by forming new anchoring villi in the open uterine veins that drain the intervillous space (21). Through serial rounds of attachment and new villous growth, the lateral placental veins enlarge, forming a marginal sinus surrounded by an investing layer of vascular smooth muscle (fig. 1-30) (59).

Between 17 and 20 weeks, the enlarging placenta/membrane sac comes in contact with and fuses with the endometrium of the opposite side of the uterus. Fusion provides the membranes with a maternal vascular supply that later assumes importance in the regulation of labor.