# 17. FORMATION AND ROLE OF PLACENTA

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**READING: Larsen, 3rd ed. pp. 20-22, 37-44 (fig. 2-7, p. 45), pp. 481-490**

**SUMMARY:**

As the developing blastocyst hatches from the zona pellucida (day 5-6 post fertilization) it has increasing nutritional needs. These are met by the development of an association with the uterine wall into which it implants. A series of synchronized morphological and biochemical changes occur in the embryo and the endometrium. The final product of this is the placenta, a temporary organ that affords physiological exchange, but no direct connection between the maternal circulation and that of the embryo.

Initially cells in the outer layer of the blastocyst, the trophoblast, differentiate producing an overlying syncytial layer that adheres to the endometrium. The embryo then commences its interstitial implantation as cells of the syncytiotrophoblast pass between the endometrial epithelial cells and penetrate the decidualized endometrium. The invading embryo is first nourished by secretions of the endometrial glands. Subsequently the enlarging syncytiotrophoblast develops spaces that anastomose with maternal vascular sinusoids, forming the first (lacunar) uteroplacental circulation. The villous placental circulation then develops as fingers of cytotrophoblast with its overlying syncytiotrophoblast (primary villi) extend from the chorion into the maternal blood space. The primary villi become secondary villi as they are invaded by extraembryonic mesoderm and finally tertiary villi as embryonic blood vessels develop within them.

During the first trimester of pregnancy cytotrophoblasts partially occlude the uterine vessels such that only plasma circulates in the intervillous space. This provides a low oxygen environment for early organ formation. Cytotrophoblasts also replace the endothelium and smooth muscle of endometrial spiral arteries, releasing them from maternal influences. The highly branched villi allow for the passage of respiratory, metabolic and other products between maternal and fetal blood systems across a barrier comprised only of embryonic tissue (a hemochorial placenta). The cytotrophoblasts and overlying syncytiotrophoblasts lining the villi are also the sources of numerous substances including peptide and steroid hormones, and growth factors.

**Note**: Further functional aspects of the placenta, including the production of steroid hormones by fetal-maternal interactions and events leading to parturition, will be considered in SBPMD.

**LEARNING OBJECTIVES:**

Be able to describe:

1. how the endometrium is prepared for implantation.
2. maternal and embryonic cellular interactions involved in the adhesion of the blastocyst to the luminal epithelium and its penetration into the endometrial stroma.
3. the establishment of the relationship between maternal and fetal blood supplies and how the area of their interface expands to meet the increasing demands of the developing embryo.
4. how failures in these processes can produce problems in pregnancy.

**GLOSSARY:**

**amnion** – amniotic cavity immediately surrounds the embryo; the amniotic membrane is derived from the epiblast and extraembryonic mesoderm

**ART** - assisted reproductive technology: inclusive term for procedures to increase the likelihood of pregnancy such as the use of ovulation-inducing drugs and in vitro fertilization

**chorion** – the fetal component of the placenta, derived from trophoblast and extraembryonic mesoderm, contains fetal blood vessels

**chorion frondosum** – region of chorion with villi whose association with the decidua basalis is the essential unit of the placenta

**chorion laeve** – abembryonic region of chorion that is without villi, therefore, smooth (laeve)

**chorionic gonadotropin** (**hCG**) – hormone secreted by the trophoblast, resembles luteinizing hormone and acts to maintain production of progesterone by the corpus luteum

**corpus luteum** - cells of ovulated follicle that remain in ovary and respond to LH by secreting progesterone and estrogens

**decidua** – the portion of the endometrium that is sloughed at menstruation and parturition, includes the region into which the embryo implants

**decidua basalis** – the portion of the decidua underlying the embedded embryo and into which chorionic villi are anchored

**decidua capsularis** – the portion of the decidua that covers the embryo as it bulges into the uterine cavity

**decidua parietalis** – the decidua that lines the remainder of the uterus

**decidual reaction** – peri-implantation changes in the endometrium: decidual cells differentiate within the stroma, accumulating abundant glycogen and lipid and synthesizing a variety of substances that promote the maintenance of the implanting embryo; the endometrium becomes highly secretory, well-vascularized and edematous

**endometrium** – the inner layer (mucosa) of the wall of the uterus

**functionalis** – region of the endometrium that is lost at menstruation

**compacta** – superficial, compact zone of the functionalis, site of implantation

**hemochorial placenta** – type of placenta in which the chorion is the only barrier between maternal and fetal blood

**inner cell mass** – (also known as the **embryoblast**) the cluster of cells in the blastocyst that will give rise to the epiblast and hypoblast (see Chapter 2), located at the embryonic pole of the blastocoel

**outer cell mass** - outer layer of cells of the blastocyst, will give rise to the trophoblast, the progenitor of the chorion

**receptivity** – state of preparedness by the endometrium for implantation (nidation) by a conceptus

**trophoblast** – derivative of cells of the outer cell mass of the blastocyst

**cytotrophoblast** – the inner proliferative layer of the lining of chorionic villi, the source of the outer syncytiotrophoblast

**syncytiotrophoblast** – the outer layer of the lining of the chorionic villi, formed by multiplication of cells of the cytotrophoblast without cytokinesis

**villus** – finger-like projection

**stem villus** – a villus that extends directly from the chorionic plate

**primary villus** – early protrusion of trophoblast into lacunae of maternal blood consisting of a core of cytotrophoblast covered by syncytiotrophoblast

**secondary villus** – the result of invasion of a primary villus by extraembryonic mesoderm

**tertiary villus** – a secondary villus that has been invaded by fetal blood vessels

**terminal villus** - a villus that terminates (floats) within the maternal blood space

**anchoring villus** – a villus that is anchored into the decidua basalis

**vitelline veins** – blood vessels that return embryonic blood from the secondary yolk sac

**yolk sac** – **primary yolk sac** is the former blastocoel now lined by extraembryonic endoderm. Extraembryonic mesoderm then migrates to line the basal side of this endoderm resulting in the formation of the **secondary (definitive) yolk sac**.

**TEXT:**

The nourishment of the embryo and later, the fetus, is accomplished through development of the placenta, which allows for the intimate relationship between (but not the confluence of) the fetal and maternal blood supplies. The placenta is formed as a result of interactions between the invading blastocyst and the tissue of the uterine wall. The process of formation of the placenta involves several critical stages and processes: **receptivity** of the uterus; **apposition** of the blastocyst to the endometrial epithelium; **adhesion** of the trophoblast to the endometrial epithelial cells; **invasion** of the epithelium, its basal lamina and the endometrial stroma; and **placentation**, i.e., the establishment of the final vascular arrangement, in humans, a hemochorial placenta.

The establishment and maintenance of the pregnancy is dependent upon signals between the embryo/fetus and the mother. Implantation has been described as a double paradox. It is a cellular paradox because it involves apposition and adhesion of the apices of two epithelia. It is an immunological paradox because it is essentially an allogenic transplant as the embryo contains both paternal and maternal genetic material. Implantation is more susceptible to mishap than is conception. Approximately 70% of all conceptions result in miscarriage. Most occur within 14 days of conception and are unrecognized by the woman.

**THE OVARY AND UTERUS**

A brief description of events within the ovary and uterus follows for the purposes of understanding implantation and formation of the placenta.

**The endometrium (Fig. 17-1)**

The uterus is made up of a wall of smooth muscle, the myometrium, lined by a thick mucosa, the endometrium, which is a layer of loose connective tissue lined by simple columnar epithelium containing glands and supplied by a specialized vascular system. Branches of arteries arise in the basal

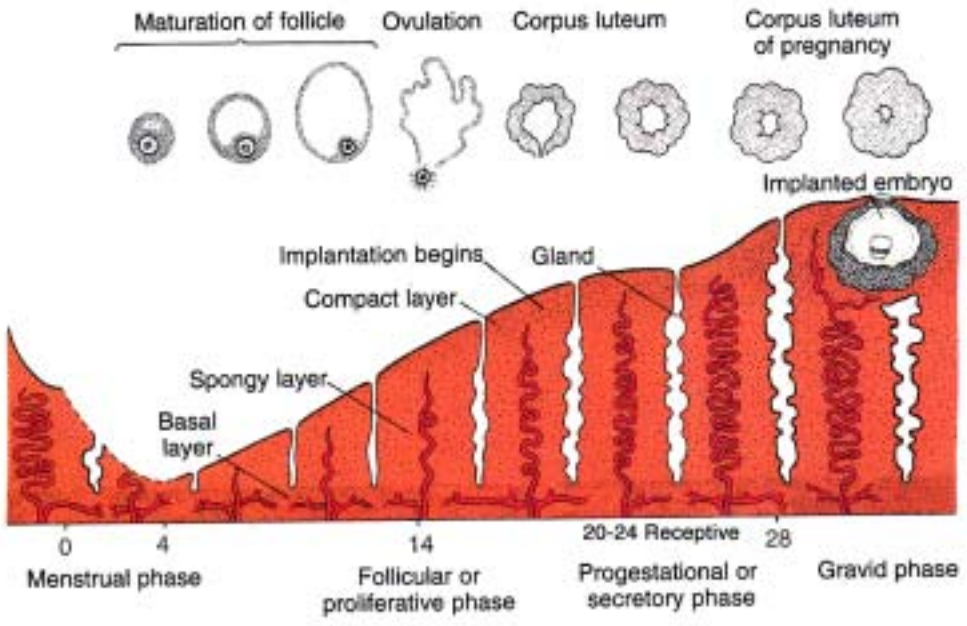


**Fig. 17-1.** Changes in the uterine mucosa correlated with those in the ovary. Implantation of the blastocyst results in development of a large corpus luteum of pregnancy. Progesterone from the corpus luteum increases the secretory activity of the endometrium. (Langman's Medical Embryology, 8th ed., TW Sadler, Lippincott Williams & Wilkins, Philadelphia (2000), p. 45 (modified).

zone of the endometrium and spiral through the overlying region, the functionalis. The characteristics of the functionalis change dramatically in response to the hormonal state over the menstrual cycle and during pregnancy. On day 1 of the 28 day cycle the functionalis begins to slough. By day 5 gonadotropin releasing hormone (GnRH) from the brain stimulates the pituitary to release two gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones promote the development of ovarian follicles. Estrogen (E) from the follicular cells promotes rebuilding of the glands and blood vessels of the endometrium (follicular phase of the ovary = proliferative phase of the endometrium). Following release of the ovum from the follicle (day 14), the remaining cells in the ovulated follicle are stimulated by LH to become the corpus luteum, which secretes high levels of progesterone (P). Progesterone causes the endometrial glands to become secretory (luteal phase of the ovary = secretory phase of the endometrium). There is a problem however, because the steroid hormones that the corpus luteum secretes inhibit GnRH secretion on which LH depends, and the corpus luteum will degenerate if there are insufficient tropic hormones. At this point the functionalis of the uterine wall breaks down. However, if there is a fertilized ovum, the corpus luteum is "rescued" because the cells of the trophoblast synthesize an analog of LH called chorionic gonadotropin (**hCG – human chorionic gonadotropin**). As the pregnancy progresses, the trophoblast also synthesizes P and E and by the third month, the pregnancy can proceed without P and E from the mother.

**Fetal-maternal interactions**

The period between days 20 and 24 of the menstrual cycle (days 6 through 10 post ovulation) provides a "window of receptivity" for implantation of a conceptus. It is essential that receptivity of the uterus be synchronized with development of the embryo. Experiments on nonhuman primates and other mammals as well as IVF (*in vitro* fertilization) observations have shown that the "implantation window" is regulated by maternal factors and is preceded and followed by refractory periods. This is discussed further below.

**The decidual reaction**

During the luteal phase, that is, following ovulation, some of the stromal cells of the endometrium enlarge and accumulate glycogen and lipid. These decidual cells disappear unless pregnancy occurs, and the corpus luteum is maintained, providing a source of progesterone. With pregnancy, continuing stimulation by progesterone and estrogen causes widespread decidualization, which is greatly amplified by the presence of the implanting blastocyst. The glands of the decidua function initially as a source of essential nutrients for the embryo until it establishes associations with the maternal blood supply. The decidua also contributes to the protection of the embryo from immunologic rejection and the uterine wall from excessive invasion by the embryo.

**The decidua (Fig. 17-2)**

The decidua is the portion of the uterine wall that is lost at parturition. Its characteristics differ in various regions of the uterus defined by the implantation site. Immediately beneath the embryo the chorionic villi anchor into the region known as the decidua basalis. This forms part of the placenta. The thin layer of endometrium that surrounds the implanted embryo is the decidua capsularis. By 20 weeks this fuses with the endometrium lining the remainder of the uterus, the decidua parietalis, obliterating the uterine lumen.

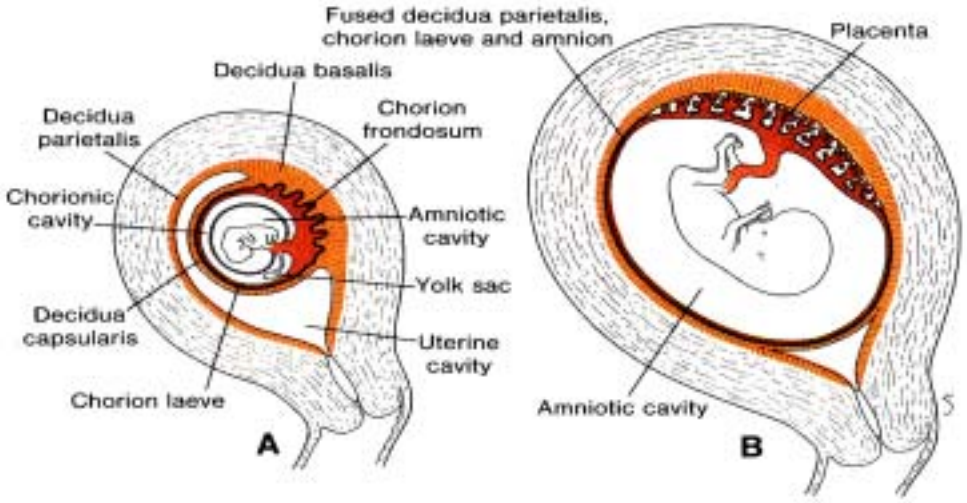


**Fig. 17-2.** The decidua and fetal membranes. A., the end of the 2nd month and B., the end of the 3rd month. Sadler, TW, Langman's Medical Embryology 8th ed., Lippincott, Williams & Wilkins, Philadelphia (2000), p. 140.

**PLACENTA**

The first step in formation of the placenta is **implantation**. This involves a series of events**: apposition, adhesion** and **invasion.** In humans (and other primates and rodents) the embryo becomes completely embedded within the endometrium and the implantation is termed **interstitial**.

**Apposition (Fig. 17-3)**

The blastocyst enveloped in its zona pellucida and surrounding follicle cells reaches the lumen of the uterus by day 4-5 post fertilization (day 18-19 of the menstrual cycle). At about day 5-6.5, the trophectoderm begins to differentiate. At the embryonic pole the underlying mitotic, diploid layer of the

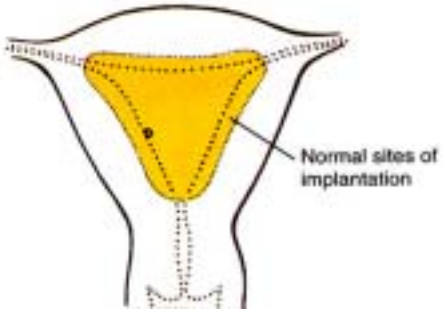


**Fig. 17-3.** Normal sites of implantation in the uterine wall (generally dorsally). Larsen, WI, Human Embryology, 3rd ed., Churchill Livingstone, New York (2001), p. 22 (modified).

trophectoderm, the **cytotrophoblast**, produces a superficial polyploid, nonmitotic syncytial layer, the **syncytiotrophoblast**. This syncytiotrophoblast is apposed to the uterine wall as the embryo hatches from the zona pellucida.

The normal site of this interaction is the outer compact zone of the endometrium in the upper 2/3 of the body of the uterus (usually in the dorsal wall). The blastocyst at this stage is about 0.1-0.2 mm in diameter and the mucosa into which it implants is about 5 mm thick. The slit-like cavity of the uterus is minimal (only about 1 mm antero-posteriorly) due to the edematous mucosa. It has been postulated that the narrowing of the uterine cavity creates a physical retention system, pressing the blastocyst against the compact zone of the endometrium.

Other implantation sites are termed "**ectopic**" and pose a variety of problems. Tubal pregnancies (within the Fallopian tube - frequently due to closure of the oviduct following pelvic inflammatory disease) are life-threatening, as growth of the embryo will cause tubal rupture around the 8th week. Implantation in the opening to the cervix (the cervical os) is called placenta praevia and results in severe bleeding during pregnancy. If the fertilized ovum escapes from the infundibulum of the oviduct, implantation can also occur at sites within the body cavity. These are also highly dangerous and must be surgically removed.

**Adhesion** (**Fig. 17-4**)

At the site of apposition, the process of adhesion of the blastocyst to the endometrial luminal epithelium begins. It should be said at this point that the earliest stages – adhesion and initial epithelial penetration have never been seen in humans, but events have been deduced from observations in higher

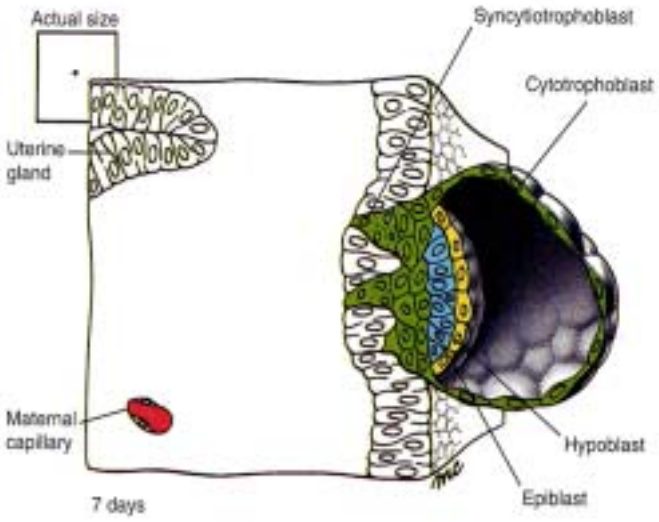


**Fig. 17-4.** The syncytiotrophoblast invades the uterine epithelium and by 8 days has expanded into the stroma. The blastocyst is nourished by uterine glands until an association is formed with the maternal vasculature. Larsen, WI, Human Embryology, 3rd ed., Churchill Livingstone, New York (2001), p. 40.

primates and other mammals. The success of ART (assisted reproductive technique) has been improved greatly through this research.

Some markers of readiness of the endometrium have been demonstrated. For instance increased secretion of a cytokine, leukemia inhibitory factor (LIF) that can be detected in uterine fluid is associated with successful implantation. A likely role for LIF is upregulation of endometrial expression of heparin-binding epidermal growth factor (HB-EGF), which in turn stimulates growth of the trophoblast and hatching of the blastocyst. Interestingly hCG from the blastocyst in turn further stimulates the production of LIF.

The luminal epithelial cells of the endometrium have a mucus-coated microvillous border, which is non-adhesive and anti-infective. The expression of the mucin, MUC-1, varies over the menstrual cycle and is upregulated by progesterone. As the embryo approaches the maternal surface, it encounters this glycocalyx. *In vitro* studies indicate that in the adhesion phase, paracrine secretions from the embryo induce a change in the ectodomain of MUC-1 molecules of the endometrial epithelial cells that are beneath and near the attached embryo. In mice only healthy embryos are able to change MUC-1 expression. This suggests that the heavy mucus layer may act as a barrier to implantation of poor quality embryos.

During the "window of receptivity" there are also changes in the cytoskeleton of endometrial epithelial lining cells such that disruptions in the terminal web cause microvilli in some cells to decrease in number and size and then to fuse or disappear. The apex of the cell then takes the form of a protrusion called a pinopode, which is thought to facilitate adhesion between the syncytiotrophoblast and endometrial epithelial cell membranes.

Throughout apposition and adhesion of the blastocyst, it is essential that the endometrium not only be protected from infection, but at the same time allow for the blastocyst to implant without rejection. The trophoblast contributes to this by expressing HLA-G, a special form of the MHC I antigen that does not stimulate resident cytotoxic T cells. In addition the populations of both T and B cells are reduced at the site of invasion.

**Invasion (Fig. 17-4)**

At the site of implantation there are changes in the polarization of the epithelial cells involving remodeling of tight junctions and adhering junctions and redistribution of apical and basolateral membrane domains. As the blastocyst invades the endometrium, the syncytiotrophoblast cells form junctional complexes with the lateral borders of the endometrial epithelial cells. Once they are firmly attached, the syncytiotrophoblasts insinuate between the epithelial cells and then burrow through their basal laminae. The decidual cells themselves may contribute to the breakdown of the basal lamina and other components of the basement membrane as laminin and collagen-IV disappear before the trophoblast reaches the basal surface of the endometrial epithelium. As they go, the syncytiotrophoblast cells also secrete agents that induce apoptosis in local endometrial cells, which they phagocytize.

**A note on secreted signaling factors, the extracellular matrix and integrins**

Successful navigation through the peri-implantation period requires highly complex maternal-fetal communication. This involves a great variety of substances that are produced by the corpus luteum, the endometrium, the pre-implantation embryo, the invading trophoblast and the developing

placenta itself. The corpus luteum is the source of the steroid hormones, progesterone and estrogen. Alterations in these hormones and their receptors are at the basis of many of the events associated with implantation and formation of the placenta. The pathways from the binding of steroid hormones to the ultimate effects are highly complex, involving modulation of the transcription of a variety of substances including signaling molecules, growth factors, integrins and components of the extracellular matrix. This is an area of active research in which there are as yet many unanswered questions.

Among the most well-studied changes are those in the integrins, which, depending upon the forms of their α and β subunits mediate cell-cell or cell-matrix attachment, invasion and migration; and through effects on the cytoskeleton, control cellular function. The αvβ3 integrin that provides binding to a wide variety of ECM molecules is maximally expressed during the window of receptivity. There are changes in integrin expression by both the endometrium and trophoblast over the course of the formation of the placenta as noted below (specific subunits that are expressed are not required for this course).

## EXTRAEMBRYONIC CAVITIES AND MEMBRANES (Fig. 17-2)

A number of membranes and cavities serve in the maintenance of the developing embryo. The amniotic cavity develops as an ectodermally lined space that will eventually surround the fetus. The primary yolk sac forms when the blastocoel becomes lined with extraembryonic endoderm. This then develops into the secondary or definitive yolk sac as acellular mesenchyme and then extraembryonic mesoderm spread along the basal lamina of the endoderm. The definitive yolk sac plays important roles in the first trimester. Its circulation (the vitelline circulation) is the first component of the blood vascular system to develop in the embryo. Vitelline veins deliver nutrients from the yolk sac to the embryo, via the hepatic portal system. In addition, the best evidence is that the first hematopoietic cells differentiate in association with the yolk sac. The allantois forms as a diverticulum from the cloaca (not depicted in the figure, but described in Chapter 18, development of the gut). This structure is important in non-mammalian vertebrates in disposing of nitrogenous wastes, but is largely vestigial in humans. The membrane that is the focus of the present discussion is the chorionic membrane, which is the embryonic constituent of the placenta. Its development is described below.

## DEFINITIVE PLACENTA - UTEROPLACENTAL CIRCULATION

### Formation of the chorionic villi (Figs. 17-5 through 17-9)

The fully developed placenta is a combination of a fetal portion, formed by the chorion (described below) and a maternal portion, formed by the decidua. The embryonic trophoblast must

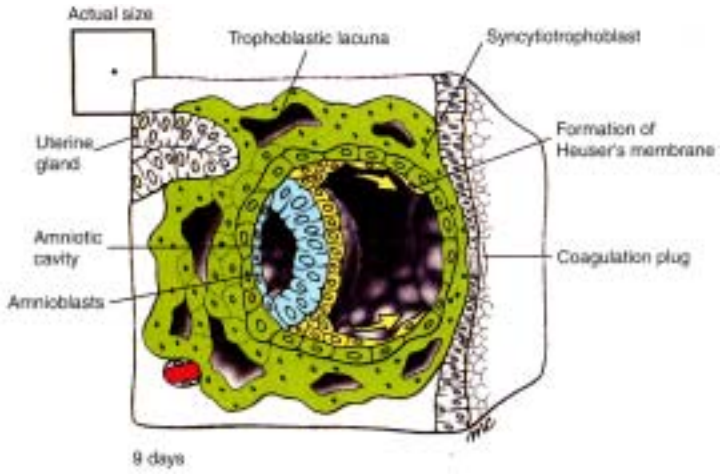


**Fig. 17-5.** By 9 days the embryo is completely implanted. Lacunae appear in the syncytiotrophoblast into which maternal blood will spill as the trophoblast invades maternal vascular sinusoids. Larsen, WI, Human Embryology, 3rd ed., Churchill Livingstone, New York (2001), p. 40.

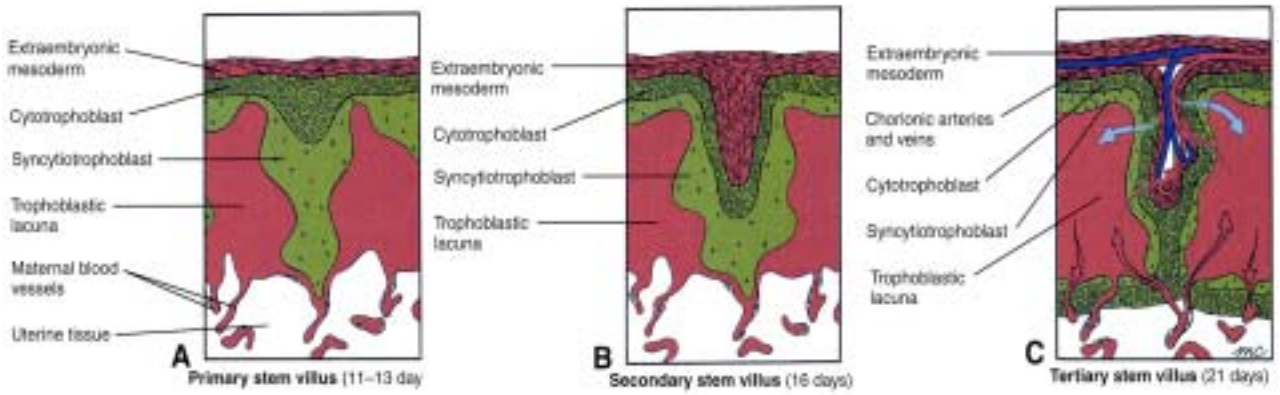


**Fig. 17-6.** Formation of the chorionic villi. **A**. Primary stem appear on days 11-13 as cytotrophoblastic proliferations bud into the overlying syncytiotrophoblast. **B.** By day 16 secondary villi are formed as the extraembryonic mesoderm (mesenchyme) invades the center of the villi. **C.** By day 21 fetal blood vessels appear within the villi, forming tertiary villi. The intervillous space contains maternal blood plasma. Larsen, WI, Human Embryology, 3rd ed., Churchill Livingstone, New York (2001), p. 45.

invade the stroma of the uterine wall and form an association with the maternal bloodstream, but not invade more deeply into the uterine wall than the upper myometrium.

There are several stages in the formation of the **uteroplacental circulation**. The first association with the maternal vasculature is at about day 9 when the invading syncytiotrophoblast develops lacunae. These anastomose with blood -filled sinusoidal spaces in the endometrium forming the first (**lacunar**) uteroplacental circulation (**Fig. 17-5**). Following this, fingers of rapidly dividing cytotrophoblast project into the syncytiotrophoblast, forming villi that are bathed in the maternal blood (**Fig. 17-6A**). These are termed **primary villi**. Beginning at the end of the second week an extraembryonic space, the chorionic cavity has been established. This cavity is bounded by extra-embryonic somatic mesoderm underlying the cytotrophoblast and the covering syncytiotrophoblast. When the primary villi become filled with mesenchyme from this mesoderm, they are called **secondary villi** (**Fig. 17-6B**). By the third week, the fetal blood and circulatory systems are forming and by d. 21 embryonic blood vessels enter the villi, making them **tertiary villi** (**Figs. 17-6C, 17-7**) At this point the fundamentals of **the villous circulation** are in place.

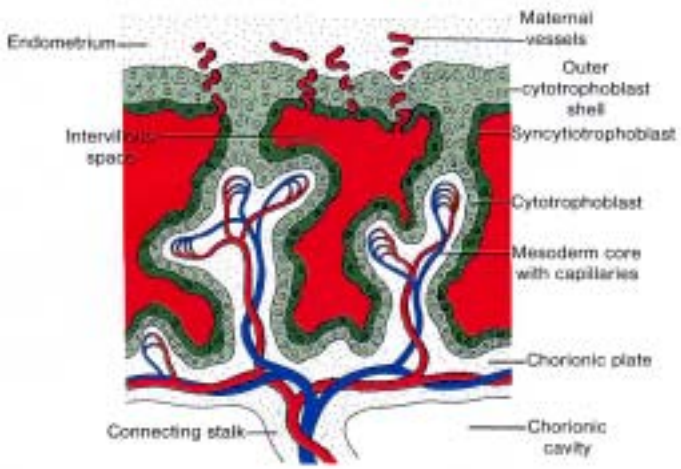


**Fig. 17-7.** 21 days, embryonic blood vessels (in the villi) exchange nutrients across the cytotrophoblast and syncytiotrophoblast with maternal plasma in intervillous space. Sadler, TW, Langman's Medical Embryology 8th ed., Lippincott Williams & Wilkins, Philadelphia (2000) p. 78.

In its final form the placenta is made up of **stem villi** that extend from the chorionic plate. These villi either float within the intervillous space (maternal blood space) as **terminal villi** or extend and attach to the decidua basalis as **anchoring villi** (**Figs. 17-8, 17-9**).

**Cytotrophoblasts in the decidual interface (Fig. 17-9)**

In the regions where the fingers of cytotrophoblast with their covering syncytiotrophoblast are attached to the decidua

(anchoring villi) cytotrophoblasts break through the syncytium forming **trophoblastic columns**. These migrating cytotrophoblasts move both deeply and laterally into the decidua, becoming the outer cytotrophoblastic shell (**arrows in Fig. 17-9A**). During this invasion, the decidual cells of the stroma secrete the growth factor, hepatocyte growth factor (HGF, also known as scatter factor, SF) that binds to its receptor, c-met, on the invading cytotrophoblasts and promotes their invasiveness. The invading cytotrophoblast cells secrete enzymes to break down the ECM. Among these enzymes are the metalloproteases (MMPs). The invasive tendencies of these cytotrophoblasts are checked by the decidua through its secretion of tissue inhibitors of MMPs (TIMPs). At the deepest regions, the decidua also impedes the movement of invasive trophoblasts both by forming a physical barrier (fibrin) and by the production of integrins and cytokines that promote trophoblast attachment rather than invasion. The depth of invasion is limited to the upper third of the myometrium in part by the action of a resident special class of natural killer (NK) cells that induce apoptosis in the extravillous cytotrophoblasts.

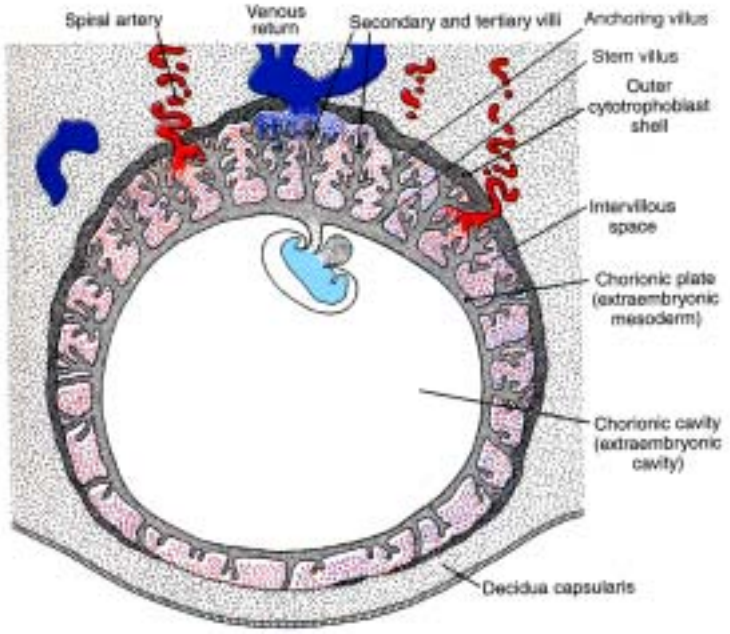


**Fig. 17-8.** 8 weeks, embryo surrounded by amnion is attached to chorionic plate by connecting stalk. Intervillous space contains maternal blood plasma from the modified spiral arteries. Sadler, TW, Langman's Medical Embryology 8th ed., Lippincott, Williams & Wilkins, Philadelphia (2000) p. 137.

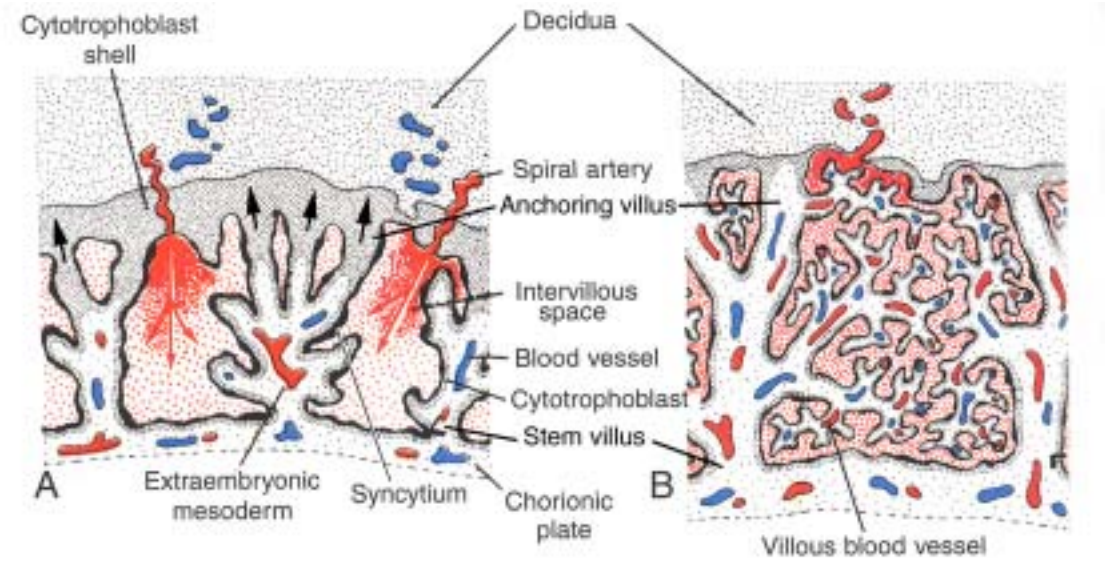


**Fig. 17-9.** Villi ramify and contents of intervillous space change. **A.** 4th week, only maternal plasma in intervillous space; **B.** 4th month, maternal whole blood in intervillous space (beginning at 12 weeks). Sadler, TW, Langman's Medical Embryology 8th ed., Lippincott, Williams & Wilkins, Philadelphia (2000) p. 138 (modified).

**Invasion of maternal blood vessels**

A final critical step in establishing the uteroplacental villous circulation involves the invasion of uterine vessels (spiral arteries) by the cytotrophoblasts. These invasive cells penetrate the blood vessels, replacing the endothelium and much of the tunica media. During this process the cytotrophoblasts again change integrin type. They now express an integrin that is a receptor for a substance that promotes blood vessel formation. In experiments in macaques (Old World monkeys that menstruate and are often used as primate models to solve problems in human reproduction) antibodies to this form of integrin have been found to block adhesion of cytotrophoblasts to endothelial cells of uterine blood vessels.

Initially a plug of fibrinoid is deposited in the lumen of the blood vessels, allowing only maternal blood plasma and not red blood cells to flow into the intervillous space, thus keeping oxygen levels low. Under these conditions anaerobic glycolysis provides the energy requirements for the early stages in organogenesis. This is thought to minimize the risk of damage to DNA by reactive oxygen species generated during aerobic metabolism. Low oxygen levels are also required for proliferation of cytotrophoblasts and for their invasion and anchoring to the decidua. By 10-12 weeks of gestation, these plugs break down and maternal whole blood then flows into the intervillous space. This results in an increase in oxygen levels and inhibition of cytotrophoblastic invasiveness. Because the walls of the spiral arteries do not contain maternal endothelium and the smooth muscle has been altered, they do not respond to hormonal and neural signals from the mother and blood is delivered steadily to the placenta.

If cytotrophoblasts are not fully invasive or if they fail to convert the spiral arteries to low resistance vessels, maternal blood flow to the placenta is not sufficient. This condition leads to secretion of vasoactive substances that result in hypertension and **preeclampsia**, with its hypoxia and ischemia, the clinical state before full-blown eclampsia (seizures).

**Final form of the placenta (Figs. 17-2, 17-10)**

The fetus hangs suspended by the umbilical cord that inserts in the chorionic plate, which in turn is anchored into the decidual basalis. The fetus is surrounded by the amnion (which has fused with the chorion in that region). On the maternal side, during the 4th and 5th months the decidua develops septa that incompletely divide the intervillous space. The result is a placenta made up of bunches of villi (cotyledons) that are partially separated from each other.

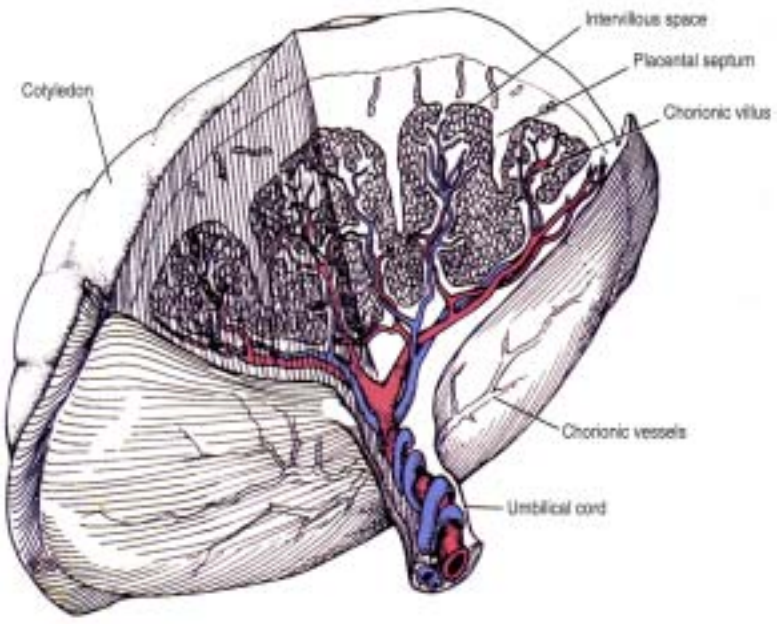


**Fig. 17-10.** The placenta is made up of cotyledons which are bunches of villi partially separated by septa of decidua. Larsen, WI, Human Embryology, 3rd ed., Churchill Livingstone, New

**The barrier between maternal and fetal blood (Fig. 17-11)**

The fully formed human placenta is termed **hemochorial** because the maternal blood is separated from the fetal blood only by elements of the chorion. The components of the barrier between

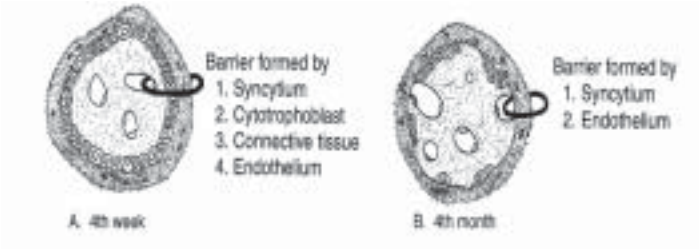


**Fig. 17-11.** The placental barrier between maternal and fetal blood. **A.** At 4 weeks; **B.** At 4 months. Sadler, TW, Langman's Medical Embryology 8th ed., Lippincott, Williams & Wilkins, Philadelphia (2000) p. 138 (modified).

fetal and maternal blood are: the syncytiotrophoblast, the cytotrophoblast, the basal lamina, the fetal mesenchyme, basal lamina of the fetal capillary and the endothelium of the fetal capillary. By the 4th month, while the barrier between the maternal and fetal blood is maintained, it is further diminished as the cytotrophoblast is reduced and finally almost completely lost.

**Summary: Functions of the placenta**

The placenta is a surrogate respiratory, excretory, and digestive organ for the fetus. It also plays a major role in the synthesis and regulation of hormones. In the case of steroid hormone production, there is an obligatory fetal-maternal interchange whereby precursors from the mother are transferred to sites containing processing enzymes, first in the placenta and then in the fetal adrenal gland. This topic will be revisited in SBPMD.

**TIMELINE**

**Post Fertilization – embryonic day/week**

| | |
|---|---|
| d. 4-5 | blastocyst reaches uterine lumen |
| d. 5-6.5 | apposition, syncytiotrophoblast forms |
| d. 7 | adhesion/implantation |
| d. 8 | hCG detectable in mother's serum |
| d. 9 | embryo completely implanted, lacunae in syncytiotrophoblast |
| d. 11-13 | primary stem villi |
| d. 14 | cytotrophoblasts partially occlude spiral arteries, maternal blood circulates (plasma only, no cells) |
| d. 16 | secondary villi by invasion of extraembryonic mesoderm |
| d. 21 | tertiary villi (fetal vessels) |
| 8 weeks | end of embryonic period |
| 12 weeks | maternal whole blood (cells and plasma) flow to placenta via converted spiral arteries |