3. PLACENTA

3.1 PLACENTA:

Placenta is a feto-maternal organ which is a primary site of nutrient and gas exchange between the mother and fetus.\textsuperscript{15}

![Figure 1](image_url)

After fertilization and implantation is accomplished syncytiotrophoblast secretes a hormone called human chorionic gonadotrophin. This hormone prolongs the life of corpus luteum which continues to secrete oestrogen and progesterone during approximately the first two months of pregnancy. Thereafter these and other hormones are province of definitive placenta. Menstruation does not occur and endometrium is now known as decidua of pregnancy. Decidua thickens further to form a suitable nidus for the conceptus.

As the blastocyst implants the syncytiotrophoblast digests and invades the endometrium including glands and walls of maternal blood vessels. Syncytiotrophoblast rapidly thickens towards embryonic pole and gradually thinner over the rest of the wall. After about 9-11 days of pregnancy lacunar spaces and microvillus lined clefts develop in syncytiotrophoblast. As the conceptus grows these lacunae enlarge to form an initial intervillous space. Microvillous trophoblastic walls are converted into an irregular
labyrinth which is further invaded first with cytotrophoblast and then with mesenchyme to form a radial array of secondary placental villi. Villous strands extend from the syncytial layer of chorion across the intervillous space. A layer of cytotrophoblast lined by vascularized fetal mesenchyme is present on their embryonic aspect. The villous strands extend to the layer of peripheral trophoblast which is opposed directly by excavated maternal tissues. Extravasated maternal blood continues to enter the intervillous space through spaces in layer of peripheral trophoblast.

As the intrasyncytial lacunae are developing a column of proliferating cytotrophoblast extends from chorionic plate through the syncytiot to make direct contact with the maternal stroma. Cytotrophoblast proliferation further occurs laterally so that the neighboring outgrowths meet to form a spherical cytotrophoblastic shell around the conceptus. Capillaries from within the mesenchymal core now establish connections with the radicles of umbilical vessels in the general mesenchyme of chorion. Each villus now consists of vascularized mesenchymal core covered by a layer of cytotrophoblast which is again en sheathed by a layer of syncytiot. These are now called the tertiary villi. Near the maternal interface these villi do not contain mesenchymal core but solid cytotrophoblastic cell columns which are continuous peripherally with the cytotrophoblastic shell. The developing placenta thus consists of tertiary chorionic villi connected to the maternal stroma by cytotrophoblastic columns called as anchoring villi.

Expansion of whole conceptus is accompanied by radial growth of villi and integrated tangential growth of trophoblastic shell and branching villous tree continuing till term. Eventually each stem villus forms a complex consisting of single trunk attached to the chorion at its base, from which arise the second and third order branches.

Each terminal villus commences as a syncytial outgrowth which is invaded by cytotrophoblastic cells which then develops a core of fetal mesenchyme and is finally vascularized by fetal capillaries. Terminal villi are specialized for exchange between the fetal and maternal circulations. Terminal villi continue to form and branch, projecting in all directions in intervillous space within the confines of definitive placenta throughout gestation.15
3.1.1 SHAPE AND SIZE OF PLACENTA:

A mature placenta is a flattened discoid mass which is circular or oval in outline and measures about 15 to 20 cms in diameter, 2 to 3 cms in thickness and weighs about 500 to 600 grams at term.\textsuperscript{16}

An expelled placenta consists of two surfaces:

- Fetal surface
- Maternal surface

**Fetal surface**: Macroscopically fetal surface or inner surface is covered with amnion and appears smooth, shiny and transparent. It is closely applied to the subjacent chorion which is mottled in appearance. The umbilical cord is attached near the center of this surface and branches of umbilical vessels radiate out under the amnion from this point. The veins are deeper and larger than the arteries. Fetal part of placenta is formed by villous chorion, chorionic villi arise from it and project into the intervillous space containing maternal blood.

**Maternal surface**: Maternal surface is granular in appearance and is divided into 15 to 30 lobes by a series of grooves. These lobes are termed as cotyledons. These grooves correspond to bases of incomplete placental septae which become increasingly prominent after third month. These placental septae extend from maternal aspect of intervillous space towards the chorionic plate, but they do not quite reach the chorionic plate. These septae are complex structures and comprise of components of cytotrophoblastic shell, residual syncytium, maternally derived material including decidual cells, occasional blood vessels, gland remnants, collagenous and fibrinoid extracellular matrix. The maternal part is formed by decidua basalis.\textsuperscript{15}

3.1.2 PLACENTAL TISSUES ARE ARRANGED AS:

A. Chorionic plate

B. Basal plate

C. Intervillous space
A. Chorionic plate: On the fetal aspect its covered by amniotic epithelium. Stromal side of which has connective tissue layer carrying main branches of umbilical vessels. Adjacent to this is diminishing layer of cytotrophoblast and inner syncytial wall of intervillous space. Fusion between mesenchyme covered surfaces of amnion and chorion forms the connective tissue layer. This connective tissue is more fibrous and less cellular than the Wharton’s jelly of umbilical cord, except near the large vessels. The large vessels radiate and branch from the cord attachment until they reach the bases of the trunks of the villous stems. These branches of large vessels then enter and arborize within the intermediate and terminal villi.

B. Basal plate: The basal plate is thinned and progressively modified throughout second half of pregnancy. There is relative diminution of decidual elements and increased deposition of fibrinoid.

From fetal to maternal aspect it consists of:

- **Outer wall of intervillous space**: This comprises of syncytium, cytotrophoblast and fibrinoid matrix.
- **Rohr’s stria of fibrinoid**: This stria is irregularly interconnected. Strands pass from Nitabuch’s stria into the adjacent decidua.
- **Remains of cytotrophoblastic shell**.
- **Nitabuch’s stria of fibrinoid**: Nitabuch’s stria and basal decidua contain cytotrophoblast and multinucleate trophoblast giant cells that originate from mononuclear cytotrophoblast population which infiltrates the basal decidua during the first 18 weeks of pregnancy. The penetration of these cells is as far as the inner one third of the myometrium. They are not found in parietal decidua nor in the adjacent myometrium. Thus these placental bed giant cells appear to be a differentiative end stage in the extra villous trophoblast lineage.
- **Maternal decidua**: It contains large and small decidual cells which are scattered in connective tissue framework and basal remnants of endometrial glands.

C. Intervillous space: Intervillous space is derived from lacunae that develop in syncytiotrophoblast and eventually coalesce. The maternal blood approaches the intervillous space through various layers of basal plate. Maternal blood enters this space from spiral endometrial arteries which open through the gaps in cytotrophoblastic shell.
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and discharge blood in the intervillous space. At term the walls of most spiral arteries consists of fibrinoid matrix within which cytotrophoblast is embedded. This allows expansion of arterial diameter to give an increased blood flow which is privileged in being independent of vasoconstrictors. This large space is drained by endometrial veins. The veins which drain the blood away from the space pierce the basal plate and join the tributaries of uterine veins. Numerous branch chorionic villi that arise from stem villi are continuously bathed with maternal blood that circulates through the intervillous space.\textsuperscript{15}

3.2 STRUCTURE OF PLACENTA:

Microscopically cross section of full term placenta shows cut sections of several chorionic villi.

Chorionic villi are essential structures involved in exchange between mother and fetus. Each stem villus has its base at the chorionic plate which progressively branch into intermediate and terminal villi.

Each villus has a core of connective tissue containing collagen type I, type III, type V, type VI and fibronectin. Type I collagen is often found as bundles while type III collagen fibers are thinner forming a meshwork. Collagen V and VI are found as fibers which are closely associated with type I and III. Collagen type IV and basal lamina associated molecules laminin are found in stroma in association with fetal vessels as well as in basal lamina of trophoblast. Cyto and syncytiotrophoblast overlie this matrix and are bathed by maternal blood in the intervillous space. Cohesion between the cells of cytotrophoblast is provided by numerous desmosomes. Desmosomes also provide cohesion between cyto and syncytiotrophoblast between their opposed plasma membranes.

Cytotrophoblast forms a continuous layer on the basal lamina in earlier stages but it gradually expends itself to form syncytiotrophoblast after the fourth month. As the cytotrophoblast decreases the syncytiotrophoblast becomes progressively thinner and becomes adjacent to the basal lamina over an increasingly large area. A few singly disposed cytotrophoblastic cells persist until term.

The cells of villous cytotrophoblast also known as langerhans cells are pale staining with only slight basophilia. Ultra structurally they show very few organelles and electron translucent cytoplasm. Cell organelles like a few clusters of ribosomes, narrow cisternae
of rough endoplasmic reticulum, golgi apparatus and large mitochondria are seen in the cytoplasm. Also intermediate filaments particularly associated with desmosomes are seen. Between the desmosomes the membranes of adjacent cells show an intercellular gap of 20 nm which sometimes widens to accommodate microvillous cell projections from the cell surfaces.

The syncytial cytoplasm is more strongly basophilic. It is complex and more electron dense than that of langerhans cells. Where the plasma membrane adjoins the basal lamina it shows complex infoldings into the cytoplasm. Surface bordering the intervillous space shows numerous long microvilli. Cytoplasm contains a free wealth of ribosomes, cisternae of granular endoplasmic reticulum, scattered Golgi complex, mitochondria, cytoskeleton of microfilaments, profusion of vesicles and vacuoles and numerous lysosomes and phagosomes. It is an intensely active layer across which most transplacental transport occurs. It is also responsible for the secretion of range of placental proteins into the maternal circulation which include chorionic gonadotrophin, chorionic somatomammotrophin and others.

Glycogen is present in both layers of trophoblast at all stages. Lipid droplets are also present in both layers, principally within the cytoplasm and basal lamina. These droplets diminish in number with advancing age and may represent fat in transit from mother to fetus. Membrane bound granular bodies occur particularly in cytoplasm of syncytiotrophoblast. Some of these are probably secretion granules. Lysosomes and phagosomes are concerned with degradation of materials engulfed from intervillous space.

In the immature placenta syncytial sprouts are found which represent first stages of development of new terminal villi. These later get invaded by cytotrophoblast and villous mesenchyme. Syncytial sprouts are also seen in the term placenta but the enclosed nuclei here are largely degenerative. Syncytial knots represent similar aggregates of degenerative nuclei. This represents a sequestration phenomenon which involves removal of senescent nuclear material from adjacent metabolically active areas of syncytium. These sprouts may detach and form maternal syncytial emboli. Daily a passage of some 100,000 such sprouts into the maternal circulation has been computed.
Fibrinoid deposits are found on villous surface in areas lacking syncytiotrophoblast which appears to be a repair mechanism in which fibrinoid forms a wound surface that is subsequently re-epithelialized by trophoblast. Tenascin is an extracellular matrix glycoprotein that is localized in the stroma adjacent to these sites.

Large reticulum cells, fibroblasts and large phagocytic Hofbauer cells are present in villous core. There is increase in mesenchymal collagen from network to fine fibers in early mesenchymal villi to densely fibrous stroma of stem villi of second and third trimester. Stromal channels found in immature intermediate villi is infilled by collagen after about 14th week to give the fibrous stroma characteristic of the stem villus.

The fetal vessels include arterioles and capillaries. Their endothelium contains fine cytoplasmic filaments. Pericytes may be found in close association with capillary endothelial cells. The vessels are surrounded externally by periendothelial basal lamina membrane. From second trimester onwards and later the terminal villi show dilated thin walled capillaries immediately adjacent to villous trophoblast. The two basal laminae are apparently fused to produce a vasculosyncytial interface.\textsuperscript{15}

### 3.3 PLACENTAL BARRIER

Blood in the fetal vessels is separated from maternal blood in the intervillous space by a placental barrier. Placental barrier is interposed between blood streams, but it is a selectively permeable barrier which allows water, oxygen and other nutritive substances and hormones to pass from mother to fetus and some products of excretion from fetus to mother.

#### 3.3.1 LAYERS THAT CONSTITUTE THE PLACENTAL BARRIER ARE :\textsuperscript{17}

Six components separate the fetal circulation from maternal circulation throughout the first half of gestation. These components comprise the placental barrier, they are as follows:

Both chorionic villi and chorionic plate are entirely covered by:

- Syncytiotrophoblast: It is characterized by numerous small and dark staining nuclei.
- Cytotrophoblast: Cytotrophoblast cells are present underlying the syncytiotrophoblast.
- Underlying trophoblastic basement membrane.
- Fetal loose connective tissue that constitutes the core of each villus.
- Basement membrane of fetal capillaries.
- Endothelium of fetal capillaries.\textsuperscript{17}

The thickness of placental barrier reduces progressively during gestation. After fourth month the villous syncytium becomes thinner and comes in direct apposition to subepithelial basal lamina over an increasing area. At term the cytotrophoblast layer is reduced to small fragments, thus placental barrier comprises of five layers instead of six. The fetal capillaries become dilated and approach the surface of terminal villi.\textsuperscript{15,17}

\textbf{3.4 UTEROPLACENTAL CIRCULATION:\textsuperscript{18}}

\textbf{3.4.1 FETAL CIRCULATION:} A large surface area is provided by branch chorionic villi of placenta. Exchange of materials between mother and fetus takes places through these various branch villi which arise from stem villi across very thin placental membrane. Poorly oxygenated blood leaves the fetus and passes through umbilical arteries to the placenta. These arteries further divide into various chorionic arteries before entering the chorionic villi. The blood vessels form an extensive arteriocapillary venous system within the chorionic villi which brings the fetal blood extremely close to the maternal blood. This system provides a large surface area for exchange of products between fetal and maternal blood. There is no intermingling of fetal and maternal blood cause of the placental barrier that lies between them. Thin walled veins converge to form the umbilical vein which carries oxygen rich blood to the fetus.

\textbf{3.4.2 MATERNAL CIRCULATION:} Maternal blood enters the intervillous space through 80 to 100 spiral endometrial arteries in decidua basalis. The blood flow from the spiral arteries is considerable at a higher pressure than intervillous space and is propelled in a jet like manner and spurs towards the chorionic plate which forms the roof of intervillous space. The blood flows slowly over the branch villi and allows exchange of products with the fetal blood. The blood returns through the endometrial veins to the maternal circulation.
3.5 FUNCTIONS OF PLACENTA :

The main functions of placenta is transfer of oxygen and nutrients. 18,19

3.5.1 PLACENTAL TRANSFER: Great surface area of placental membrane facilitates transport of substances in both the directions between placental and maternal blood. Factors affecting placental transfer:

- Low molecular weight substances transfer more easily than those of high molecular weight. Water soluble substances up to weight 100 and lipid soluble substances up to weight of 600 or more can cross readily. However diffusion is limited when molecular weight is more than 1000. Ionized substances cross in a very small amount irrespective of molecular weight.

3.5.2 RESPIRATORY FUNCTION:

Oxygen and Carbon dioxide: Gases like oxygen, carbon dioxide and carbon monoxide cross the placenta by the process of simple diffusion. The rate of oxygen supply to fetus is 5ml/kg/min. The placental membrane is highly permeable to carbon dioxide. These gases diffuse freely across placenta.

3.5.3 NUTRITIVE FUNCTIONS OF PLACENTA:

Water: Water freely crosses the placenta. At term it reaches to 3.5 L/h.

Glucose: Transfer of glucose is by the process of facilitated diffusion. Glucose molecule combines with a carrier protein to form a lipid soluble complex. Because of increased consumption fetal glucose levels are lower than the mother.

Amino acids: Neutral straight chain amino acids, acidic and non-essential amino acids are synthesized in the placenta and not absorbed from the maternal serum. Basic amino acids like lysine and histidine are transferred by specific transport mechanism as these amino acids have higher concentration in the maternal blood.

Lipids: Lipids cross the placenta freely by the process of simple diffusion. In early pregnancy fatty acids, triglycerides and cholesterol are directly transported from the mother to the fetus. Later they are synthesized by the fetus. Levels of arachidonic acid are
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high as they are synthesized from cholesterol in the placenta. Fetus and placenta also can synthesize fatty acids from glucose.

**Water soluble vitamins:** Fetal concentration of these vitamins is higher than that of the mother. Water soluble vitamins are absorbed by active mechanisms. Although the placenta is impervious to vitamin A fetus can synthesize vitamin A from carotene which easily crosses the placenta. The level of fat soluble vitamins is lower in fetal serum as they are transferred slowly. Iron, calcium and phosphorous cross the placenta by the process of active transport. Parathormone and calcitonin do not cross the placenta.

**Electrolytes:** Sodium and Potassium readily cross the placenta by the process of simple diffusion. The requirement of water is more by the fetus and the transfer is dependent upon osmotic and hydrostatic pressures. Hormones such as vasopressin, oxytocin and prolactin are also thought to have a role in control of water exchange.

**Drugs:** Transfer of drugs through placenta is determined by their molecular weight and affinity for lipids and ionisation. Infectious agents like rubella virus, cytomegalovirus, coxsackie and poliomyelitis can cross the placental membrane and cause fetal infection.

**Steroids:** Steroids also cross the placenta readily.

3.5.4 **EXCRETORY FUNCTION:**

Products like uric acid and urea are excreted into the maternal blood by the process of simple diffusion.

3.5.5 **IMMUNOLOGICAL FUNCTION:**

Maternal immunoglobins provide protection to the fetus against infectious agents like measles, diphtheria etc. The fetus is provided with passive immunity by these antibodies against infectious diseases for some time after birth until the neonates own immune system starts functioning.
3.5.6 ENDOCRINE FUNCTION OF PLACENTA:

Protein hormones:

Human Chorionic Gonadotrophins (hCG):

hCG is also known as pregnancy hormone. It is a glycoprotein hormone with molecular weight of 38,400 daltons and it is a glycoprotein with highest carbohydrate residue. hCG is mainly synthesized by syncytiotrophoblast of placenta after synthesis from corpus luteum ceases. hCG is also produced by fetal kidney and malignant trophoblast. In a normal pregnancy shortly after implantation hCG can be detected in urine and plasma of a pregnant woman.

Functions of hCG:

- Rescue of corpus luteum: hCG continues the production of progesterone and maintains the pregnancy until third month.
- hCG stimulation of fetal testis: The peak of secretion of testosterone by fetal testis corresponds to the same time when maternal serum has maximum levels of hCG. There is only small amount of LH secretion by pituitary so hCG acts as LH during this period and promotes male sexual differentiation by helping in production of testosterone.
- hCG stimulation of maternal thyroid.
- hCG promotes relaxin secretion by corpus luteum and it may also promote uterine vascular dilation and myometrial smooth muscle relaxation.

Human Placental Lactogen (hPL):

hPL has a prolactin like activity and it is found to be concentrated in the syncytiotrophoblast and cytotrophoblast by around second or third week after fertilization. hPL is structurally and functionally more similar to pituitary growth hormone and prolactin, but its biological activity is less. The levels of hPL in the maternal blood show gradual rise with a plateau after 35-36 weeks. It’s proportional to placental mass.
Functions of hPL:

- Lipolysis and increase in the levels of free circulating free fatty acids. This helps in production of energy for both fetal and maternal metabolism.
- Angiogenesis that is production of fetal vasculature.
- Anti-insulin action.

Other Placental Hormones:

Chorionic adrenocorticotrophins:

This is a protein which is isolated from placental tissue. It is similar to ACTH. The concentration of ACTH increases as the pregnancy advances. ACTH does not cross the placenta. The placenta might produce ACTH which is then secreted into the mother and fetus.

Relaxin:

Relaxin is a peptide hormone. It is structurally similar to insulin. There are two relaxin genes H1 and H2. H2 genes are transcribed in corpus luteum of the ovary while H1 genes are expressed on placenta, decidua and fetal membranes. Relaxin acts on myometrial smooth muscles to stimulate adenyl cyclase thus promote uterine relaxation.

Oestrogen:

Placenta produces large amount of oestrogen and this production and synthesis of hormone is dependent on the steroidal precursors in the blood. The placental syncytiotrophoblast synthesizes oestriol from its fetal precursor dehydroepiandrosterone which is a product of adrenal glands of fetus. It is then hydroxylated in the fetal liver.

Maternal conditions that affect placental oestrogen synthesis:

- Glucocorticosteroid treatment: High dose of corticosteroid administration to pregnant woman causes a reduction in placental oestrogen formation as it inhibits ACTH secretion.
- Maternal hypertensive disorders: In maternal hypertensive disorders and diabetes fetal adrenal synthesis of dihydro-epiandrosterone is impaired because of decrease
in the uteroplacental blood flow and not because of reduction in the placental functions.

- **Maternal renal disease**: Pregnant woman with pyelonephritis show low levels of oestrogen in urine. This is probably because of low renal clearance.

**Progesterone**: 

Progesterone is secreted by corpus luteum up to 6-7 weeks of gestation. Thereafter, it is synthesized by placenta. Maternal cholesterol is converted to pregnenolone in the mitochondria which is then converted to progesterone in the endoplasmic reticulum.

**Chorionic thyrotropin**: The placenta produces chorionic thyrotropin but its role in pregnancy is not yet clear.

**Parathyroid hormone related protein**: This hormone may serve as the parathyroid of the fetus.

**Human growth hormone variant**: This growth hormone variant gene is expressed in placenta. It is present in maternal plasma by 21 to 26 weeks and gradually increases in concentration by term.

**Hypothalamic like releasing hormones**: Human placenta produces hormones analogous to GnRH, TRH, CRH and somatostatin produced by the hypothalamus.