PLACENTA

Introduction:

For the nine months of its intrauterine existence, the human fetus is totally reliant on the placenta, a transient extracorporeal organ that interfaces with the mother, to sustain and protect him. This dependency is reflected in the way that various societal groups consider the placenta as a twin or guardian angel, and venerate it as a sacred object. Hence, the placenta is often accorded ritual burial, for in some beliefs the soul must be reunited with its placenta before being able to pass through to the afterlife ***(Yoshizawa, 2013)***.

The placenta is arguably the most important organ of the body, but paradoxically the most poorly understood. During its transient existence, it performs actions that are later taken on by diverse separate organs, including the lungs, liver, gut, kidneys and endocrine glands. Its principal function is to supply the fetus, and in particular, the fetal brain, with oxygen and nutrients. The placenta is structurally adapted to achieve this, possessing a large surface area for exchange and a thin interhaemal membrane separating the maternal and fetal circulations. In addition, it adopts other strategies that are a key for facilitating transfer, including remodeling of the maternal uterine arteries that supply the placenta to ensure optimal perfusion. Furthermore, placental hormones have profound effects on maternal metabolism, initially building up her energy reserves and then releasing these to support fetal growth in later pregnancy and lactation postnatally ***(Burton and Fowden, 2015)***.

Definition:

The placenta is the fetal organ providing the interchange between the mother and the fetus ***(Huppertz, 2008).***

Macroscopic anatomy of delivered placenta:

Full term placenta is a circular discoid organ with a diameter of about 22 cm, a central thickness of 2.5cm and or average weight 470 gm ***(Bouw et al., 1976).***

Term infant weights concerning seven times the placental weight. Placenta over 750gm and less than 350gm are likely to be normal ***(Molteni et al., 1978).***

Structure

In humans, the placenta averages 22 cm (9 inch) in length and 2–2.5 cm (0.8–1 inch) in thickness (greatest at the center and becoming thinner peripherally). It typically weights approximately 500 grams. It has a dark reddish-blue or maroon color. It connects to the fetus by an umbilical cord of approximately 55–60 cm (22–24 inch) in length that contains two arteries and one vein ***(Benirschke et al., 2012).***

Its surfaces are the chorionic plate that faces the fetus and to which the umbilical cord is attached, and the basal plate that abuts the maternal endometrium. Between these plates is a cavity, the intervillous space, into which 30–40 elaborately branched fetal villous trees project. Each villous tree arises from a stem villus attached to the deep surface of the chorionic plate, and branches repeatedly to create a globular lobule 1–3 cm in diameter. The center of a lobule is located over the opening of a maternal spiral artery through the basal plate. Maternal blood released at these openings percolates between the villous branches before draining into

openings of the uterine veins and exiting the placenta. Each lobule thus represents an independent maternal–fetal exchange unit ***(Benirschke et al., 2012)***.

Final branches of the villous trees are the terminal villi. These present a surface area of 12–14 m^2 at term, and are richly vascularized by a fetal capillary network. The capillaries display local dilations, referred to as sinusoids, which bring the endothelium into close approximation to the covering of trophoblast. This is locally thinned, and the diffusion distance between the maternal and fetal circulations may be reduced to as little at 2–3 mm. The morphological resemblance of these structures, termed vasculosyncytial membranes, to the alveoli of the lung has led to the assumption that they are the principal sites of maternal–fetal exchange. Terminal villi are formed primarily from 20 weeks of gestation onwards, and elaboration of the villous trees continues until term ***(Benirschke et al., 2012)***.

The epithelial covering of the villous tree is the syncytiotrophoblast, a true multinucleated syncytium that presents no intercellular clefts to the intervillous space. This arrangement may assist in preventing the vertical transmission of pathogens from the maternal blood, but may also facilitate regional specializations of the syncytiotrophoblast. Because of its location, the syncytiotrophoblast is involved in many of the functions of the placenta, such as the synthesis and secretion of steroid and peptide hormones, protection against xenobiotics and active transport. Hence, it has a high metabolic rate, and accounts for approximately 40% of the total oxygen consumption of the feto-placental unit ***(Robbins et al., 2010)***.

The syncytiotrophoblast is a highly polarized epithelium, bearing a dense covering of microvilli on its apical border. The projections provide

a surface amplification factor of 5–7_ for insertion of receptor and transporter proteins.

The syncytiotrophoblast is a terminally differentiated tissue, and its expansion during pregnancy is achieved by the fusion and incorporation of underlying mononuclear progenitor cytotrophoblast cells that rest on the underlying basement membrane ***(Benirschke et al., 2012)***.

The umbilical cord forms in the region of the body stalk and becomes covered by the expanding amnion. Eventually embryonic structures and the right umbilical vein disappear from the cord, leaving two arteries and one vein. The remnant of the yolk sac, a 4 mm calcified yellow nodule, lies between the amnion and chorion ***(Kaplan, 2007).***

The umbilical cord is usually attached near the center of the fetal surface and the branches of the umbilical vessels radiate out under the amnion form this point, the veins being deeper and larger than the arteries. Beneath the amnion and close to the attachment of the umbilical cord, the remalus of the yolk sac can sometimes be identified as a minute sac with a fine thread (a vestige of vitello-intestinal duct) attached to it ***(Cunningham et al., 2005).***

The umbilical cord normally contains three vessels, two arteries and the persisting left umbilical vein. The absence of one umbilical artery (SUA) occurs in about 1% of deliveries. In the most placentas the arteries fuse in the last few centimeters above the fetal surface, so the finding of only two vessels should be confirmed in several areas. About 20% of babies missing one artery will have other major congenital anomalies which are usually apparent in the neonatal period. ‘‘Non-malformed’ babies with SUA are slightly small and have increased perinatal mortality ***(Kaplan et al., 1990).***

An obvious feature of the umbilical cord is its length. Cord length increases throughout gestation but more slowly in the 3rd trimester**.** Fetal activity and traction on the cord increase its Length**.** Long cords (70 cm) are associated with knots and fetal entanglement ***(Baergen, 2007).*** It is not clear if the entanglements occur because the cord is long, or the cord length is increased due to traction when an entanglement occurs. Abnormally long cords may have a genetic component. A minimum cord length of 32 cm is believed necessary for normal vaginal delivery ***(Kaplan, 2007).***

The umbilical cord usually twists counterclockwise (‘‘left’’ twist)**.** The reason for this is unclear. Cords without twists are associated with increased perinatal morbidity and with single umbilical arteries. Normally there is one twist every few centimeters ***(Machin et al., 2000).***

Excessive twisting is associated with fetal death or morbidity. True torsion and stricture also occur, particularly near the body wall ***(Peng et al., 2006).***

The umbilical cord may insert into central villous tissue, at the margin of the placenta, or into the membranes (velamentous). Central and eccentric cord insertions are of little consequence and location is largely due to differential placental growth. Marginal and velamentous insertions are considered abnormally ***(Kaplan, 2007).***

Babies with such cords are smaller on average. Particularly significant is the presence of vessels unsupported by Wharton jelly which are at risk for compression and tearing, particularly if over the cervical os (vasa previa). Rupture of a velamentous vessel prior to fetal delivery leads to rapid, often catastrophic fetal blood loss. Velamentous vessels occur with succenturiate lobes and occasionally at the edge of a placenta with otherwise normal cord insertion ***(Kaplan, 2007).***

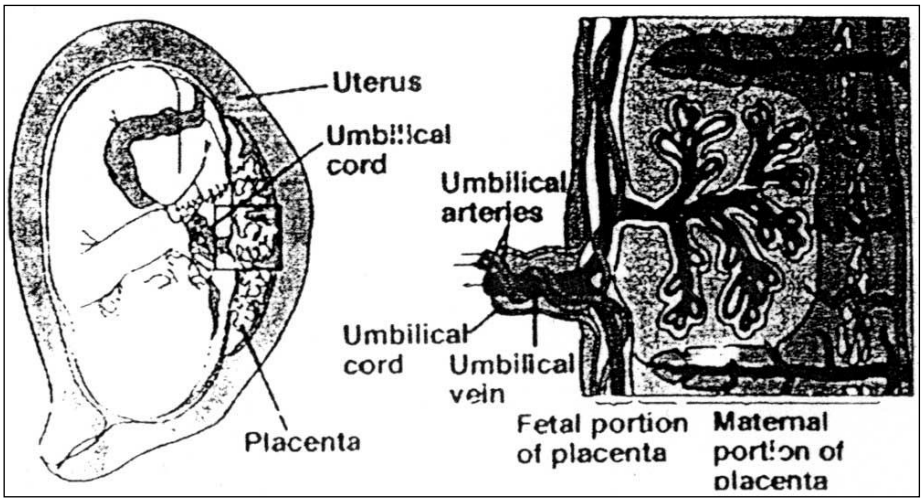

Figure (1): The placenta and the umbilical cord ***(Cunningham et al., 2005).***

The Chorion

On the twelfth postconception day, implantation may be considered finalized. At that time extraembyronic mesodermal cells derived from the primitive streak have begun to migrate on top of the inner surface of the cytotrophoblast cells, the combination of the extraembyronic mesoderm and cytotrophoblasts is termed chorion ***(Endres, 1988).***

At the placental margin chorionic and basal plates merge and form the smooth chorion, the fetal membranes or the chorion laeve. The chorion laeve is composed of three layers: the amnion with its epithelium and mesenchyme; the chorion with a layer of mesenchyme and a layer of extravillous trophoblast; and the decidua capsularis ***(Huppertz, 2008).***

Development of the Placenta:

There is stages for placental development:

1-Preimplantation Stage:

During human development, between the stages of the morula and blastocyst (days 4-5 postconception) the trophoblast differentiate. After that the blastocyst consists of an inner cell mass that is surrounded by a single layer of mononucleated trophoblasts. This outer layer surrounds, the embryoblast, blastocoele and the blastocyst cavity.

Later during pregnancy the trophoblast gives rise to larger parts of the placenta and fetal membrane, while the inner cell mass gives rise to the embryo and umbilical cord as well as the placental mesenchyme. At about 6-7 day postconception, the blastocyst hatches from the zona pellucida and attaches to the uterine epithelium ***(Aplain, 2000).***

2- Prelacunar Stage:

Only the polar trophoblast which overlies the inner cell mass seems to be able to finally lead to implantation ***(Boyd and Hamilton, 1967).***

As soon as the blastocyst has firmly attached to the uterine epithelium, the polar trophoblast undergoes differentiation into first oligonucleated syncytiotrophoblast and cytotrophoblast. At that stage the syncytiotrophoblast displays an invasion phenotype which penetrates the uterine epithelium ***(Boyd and Hamilton, 1967).*** The cytotrophoblast divides rapidly and fuses with the syncytiotrophoblast resulting in a continuous expansion of syncytiotrophoblast ***(Potgens et al., 2002).***

3. Lacunar Stage:

Eight days after conception, fluid filled spaces occur within the syncytiotrophoblast and coalesce to form larger lacunae, the remaining syncytiotrophoblastic masses between the lacunae are termed trabeculae.

So three fundmental zones of the placenta can be defined: the early chorionic plate facing the embryo the lacunar system together with the trabeculae developes into intervillous space and villous trees and the

primitive basal plate in contact with the maternal endometrium ***(Hertig et al., 1956).*** On the twelfth postconception day, implantation may be considered finalized.

The embryo and its surrounding tissues are completely embedded within the endometrium. The syncytiotrophoblast, displays developmental gradients: It is thicker with better developed lacunae underneath the embryonic pole, the site of first invasion. The thinner parts are more distal, towards the anembryonic pole, with smaller lacunae and less developed trabeculae ***(Luckett, 1978).***

4. Villous stage:

At about 13 days postconception the primary villi formed by syncytiotrophoblastic protrusions into the trabeculae. The mesenchymal cells penetrate into the primary villi giving them mesenchymal core and transforming them into secondary villi.

At about 20 days postconception the first blood cells, endothelial cells develops transforming the secondary villi into tertiary villi ***(Dempsey et al., 1972).***

Fetal Surface of the Placenta:

The chorionic plate represents the fetal surface of the placenta which in turn is covered by the amnion**.** The umbilical cord inserts in an eccentric position into the chorionic plate ***(Huppertz, 2008)***.

Maternal Surface of the Placenta:

The basal plate represents the maternal surface of the placenta. It is an artificial surface, which emerged from the separation of the placenta from the uterine wall during delivery. The basal plate is a colourful mixture of fetal extravillous trophoblasts and all kinds of maternal cells of the uterine decidua. A system of flat grooves or deeper clefts subdivides the

basal plate into 10–40 slightly elevated regions called lobes. Inside the placenta, the grooves correspond to the placental septa, which only trace the lobar borders as irregular pillars or short sails. The lobes that are visible on the maternal surface of the placenta show a good correspondence with the position of the villous trees arising from the chorionic plate into the intervillous space. In a full-term placenta, 60–70 villous trees (or fetal lobules) arise from the chorionic plate. Thus, each maternal lobe is occupied by one to four fetal lobules ***(Kaufmann, 1985).***

The occurrence of a single villous tree occupying a single lobe was defined as placentone ***(Kaufmann, 1985).***

Function of the Placenta:

The primary function of the placenta is to act as an interface between mother and fetus that allows, and even promotes, fetal growth and development and to contribute to the maternal cardiovascular adaptations of pregnancy ***(Blackburn, 2013)***. Appropriate perfusion of the placenta is necessary for its critical endocrine and exchange functions. Normally, the physiological remodeling of spiral arteries reduces maternal blood flow resistance and increases uteroplacental perfusion to meet the requirements of the growing fetus in normal pregnancy ***(Cross et al., 2002).***

The programming power of the placenta (Developmental Programming):

The placenta is not just a passive organ for the materno-fetal transfer of nutrients and oxygen. There is now clear evidence that the placenta is not just a passive conduit from mother to fetus, but that it is able to respond

to supply signals arising from the mother and demand signals emanating from the fetus ***(Burton and Fowden, 2012)***. Studies show that the placenta can adapt morphologically and functionally to optimize substrate supply, and thus fetal growth, under adverse intrauterine conditions. These adaptations help meet the fetal drive for growth, and their effectiveness will determine the amount and relative proportions of specific metabolic substrates supplied to the fetus at different stages of development. This flow of nutrients will ultimately program physiological systems at the gene, cell, tissue, organ, and system levels, and inadequacies can cause permanent structural and functional changes that lead to overt disease, particularly with increasing age ***(Sferruzzi-Perri and Camm, 2016)***.

Anticoagulant activity — To prevent stasis and coagulation of blood in the low velocity intervillous space, the trophoblast actively secretes substances (ADPase, nitric oxide and carbon monoxide) that prevent platelet and leukocyte adhesion and aggregation to the trophoblast surface ***(Myatt, 2002)***. The trophoblast surface also has anticoagulant activity. Annexin A5, a member of the Ca(2+)/phospholipid-dependent protein family, has been proposed as a regulator of thrombosis and homeostasis on the villous trophoblast of the placenta ***(Krikun et al., 1994)***.

Metabolic and Endocrine Functions :

Metabolic functions — The placenta is capable of synthesizing glycogen and cholesteroL which are energy sources to the developing fetus.

Glycogen synthesis — The placenta is capable of synthesizing amounts of glycogen, which it stores as an energy reserve. The uptake of glucose from the maternal circulation is a rate limiting step in this process, which involves a series of enzymes and regulators. Of particular

importance is the enzyme glycogenin, which is co-expressed with high affinity GLUT-3 transporter in the endothelium, basal decidua, and invading extravillous trophoblast of the human placenta ***(Hahn et al., 2001).***

Cholesterol synthesis — The demands for cholesterol in the fetus are high and in early pregnancy, maternal cholesterol contributes substantially to this requirement. In late gestation, the fetus itself synthesizes cholesterol from placental stores of fatty acids established from maternal body fat accumulation in early pregnancy ***(Herrera et al., 2006).*** Placental cholesterol is an important precursor for placental production of progesterone and estrogens.

Protein metabolism — Protein metabolism in the placenta is largely governed by the demands of growth throughout gestation. At week 10, placental protein production is approximately 1.5 g per day, but by term this figure rises to 7.5 g daily ***(Beaconsfield et al., 1980).***

Lactate - Lactate, a waste product of metabolism, is produced in large quantities by the placenta and therefore needs to be efficiently removed. L-lactate transporters are active on the microvillous membrane of human placenta and are present on the basal membrane ***(Settle et al., 2004).***

Endocrine function — The placenta acts as an important endocrine organ and is responsible for synthesis and selective transport of hormones and neurotransmitters into both the fetal and maternal circulation ***(Bonnin, 2011)***. The hormones produced by the placenta can be split into two categories:

1-Peptide hormones — The main site of production of the placental hormones is t1-trophoblast of the chorionic villi.

Human chorionic gonadotropin — HCG is secreted by the syncytiotrophoblast into the maternal blood, where it maintains the endocrine activity of the corpus luteum (ie, synthesis of progesterone during the early stages of pregnancy). It can be detected in maternal serum as early as day 8 after conception and reach their maximum level at week 8 of gestation. By week 13, the level drops dramatically and reaches a low steady state. By this time the placenta itself produces enough progesterone to support pregnancy ***(Blackburn, 2013)***.

Human placental lactogen — hPL is a single chain peptide hormone synthesized by the trophoblast and released into the maternal blood. The principal action of hPL is to increase the supply of glucose to the fetus by decreasing maternal stores of fatty acids.

Insulin-like growth factors — There are three ligands; insulin, IGF-I and IGF-2, at least four receptors and six IGF binding proteins (IGFBPs). Thus the IGF axis is a complex signaling pathway that is a major regulator of growth in both the fetus and postnatally. IGF-2 is the predominant growth factor and acts by binding to the IGF-1 receptor and initiating signaling cascade that induces cellular proliferation, survival, and growth ***(Randhawa and Cohen, 2005).***

Corticotropin releasing hormone — CRH is a 162 amino acid peptide that is synthesized in syncytiotrophoblast. Glucocorticoids stimulate placental CRH expression (but inhibit hypothalmic CRH), whereas progesterone and estrogen inhibit CRH. CRH concentration in the maternal circulation increases exponentially throughout gestation, but it is bound to a CRH binding protein (CRHBP) secreted by liver, so there is no CRH effect on the maternal pituitary. CRH secreted into the fetal circulation may drive increased cortisol production, maturation of the fetal lung, and increased surfactant production. CRH and the related protein

urocortin are also vasodilators of the fetal-placental circulation ***(Clifton et al., 1994 & 1995).***

Vascular endothelial growth factor and placental growth factor — VEGF is synthesized in villous trophoblast and macrophages, where it is then secreted into the maternal circulation and acts via two receptors, VEGF-R1 (FLT) and VEGF-R2 (KDR), which are found in villous vascular endothelium ***(Charnock-Jones et al., 1994).*** The action of VEGF secreted into maternal plasma is negated by binding to a soluble binding protein sFLT-1. In the placenta, VEGF acting via FLT-1 and KDR is thought to be involved in branching angiogenesis in early pregnancy. PIGF is produced in villous syncytiotrophoblast and the media of large villous vessels and also acts via VEGF-R1 and -R2. PIGF acts via FLT-1 in non-branching angiogenesis in the last trimester of pregnancy and expression is down-regulated by hypoxia, suggesting that oxygen tension may regulate the balance of VEGF and PIGF and thus, the effects seen ***(Shore et al., 1997).***

2- Steroid hormones — The steroid hormones comprise a group of molecules all derived from a common precursor, cholesterol. Steroid hormones are lipophilic molecules, which are protein bound in the bloodstream and can readily cross the bilipid membrane of cells.

A) Progesterone — Progesterone is necessary for the maintenance of a quiescent, a non-contractile uterus. The hormone has anti-inflammatory and immunosuppressive functions which protect the conceptus from immunological rejection by the mother. Initially, progesterone is produced by the corpus luteum in order to prepare the endometrium for implantation of the conceptus. Around 35 to 47 days post ovulation, the placenta takes over progesterone production (luteo placental shift) and the levels are sufficient to solely support the maintenance of pregnancy ***(Blackburn, 2013)***.

B) Estrogens — Estrogens are secreted by the corpus luteum and the adrenal cortex, as well as the placenta. The maternal, and primarily the fetal, blood streams that perfuse the placenta provide dehydroepiandrosterone sulfate (DHEAS), the substrate for estrone and estradiol, and 16-hydroxy-DHEAS, the substrate for estriol. Large amounts of DHEAs are secreted by the fetal adrenal glands and converted to estrogens in the placenta ***(Siiteri, 2005).***

C) Glucocorticoids — Glucocorticoids play a crucial role in regulation of organ development and maturation. However, fetal exposure to excessive maternal glucocorticoids may cause growth restriction. The placenta regulates exposure of the fetus to glucocorticoids by the 11ß-hydroxy-steroid dehydrogenase enzymes which catalyze reduction (11ß-HSD1) or oxidation (11ß-HSD2) of glucocorticoids. 11ß-HSD2 is located throughout the syncytiotrophoblast layer where its expression increases with gestational age ***(Murphy and Clifton, 2003).*** An increase in the ratio of 11ß-HSD2 to 11ß-HSD1 in placental membranes near term is associated with a switch in placental glucocorticoid metabolism, which may be responsible for the maturation of the fetal hypothalamic-pituitary-adrenal axis ***(Pepe et al., 2001).***

D) Imprinted Genes — Imprinting refers to the differential expression of genetic material depending on whether it was inherited from the male or female parent. Imprinted genes may have a role in the fetal demand for, and the placental supply of, maternal nutrients ***(Reik et al., 2003).***

Placental Transfer — Appropriate in utero growth is essential for offspring development and is a critical contributor to long-term health. Fetal growth is largely dictated by the availability of nutrients in maternal circulation and the ability of these nutrients to be transported into fetal

circulation via the placenta. Substrate flux across placental gradients is dependent on the accessibility and activity of nutrient-specific transporters. Changes in the expression and activity of these transporters is implicated in cases of restricted and excessive fetal growth, and may represent a control mechanism by which fetal growth rate attempts to match availability of nutrients in maternal circulation ***(Brett et al., 2014)***.

The syncytiotrophoblast (SCTB) layer of the placenta is the main site of exchange for nutrients and gases between the maternal blood stream and the fetus. It constitutes the transporting epithelium of the placenta, with two polarized membranes, the microvillous membrane (MVM) facing maternal circulation and the basal plasma membrane (BM) facing the fetal capillary, and thus the SCTB constitutes a barrier and rate-limiting step of the transport of nutrients into fetal circulation ***(Jansson and Powell, 2013)***. Nutrients predominantly enter fetal circulation through nutrient-specific transport proteins located within the MVM and BM ***(Larque et al., 2013 and Lager and Powell, 2012)***.

There are several mechanisms by which transfer occurs:

Solvent drag — Solvent drag is the movement (bulk flow) of water in which solutes and nutrients are dissolved. Bulk flow has been demonstrated in the perfused human placental cotyledon in response to hydrostatic pressure changes ***(Brownbill et al., 2000)***.

Simple diffusion — Simple diffusion is the passive transfer of solutes driven by concentration and electrical gradients. All solutes are transferred by diffusion, but the relative contribution is dependent on molecular properties. As an example, lipophilic molecules, such as

respiratory gases, are readily exchanged by simple diffusion ***(Sibley and Boyd, 2004).***

Transcellular transfer — This type of transfer utilizes transport proteins in the microvillous or basal membranes of the syncytiotrophoblast. There are three types:

Channels — These proteins form water-filled pores in the plasma membrane through which can diffuse down an electrochemical gradient. This allows transport charged hydrophilic/substances, which are insoluble in lipids. Aquaporins are an example of channels that function in the transport of water and small molecules, and are essential for fetal development ***(Liu and Wintour, 2005).***

Facilitated diffusion — These transporters are saturable carrier proteins, which are independent of metabolic energy.

Carrier mediated active transport — Primary active transport utilizes ATP to move solutes against a gradient, Na(+) K(+) ATPase and Ca2(+)ATPase are two examples. Secondary active transport utilizes concentration gradients across the cell that are set by the primary system, Na+ amino acid co-transport and the Ca(2+)/ Na(+) exchanger are examples. Transport ATPases are known to be present in human placenta. These include the Na(+): K(+) pump (Na(+)K(+)ATPase), which is localized to the microvillous and basal membrane and a high affinity Ca(2+)ATPase located on the basal membrane ***(Johansson and Powell, 2000).***

Transfer of specific substances

1- Respiratory gas exchange — Both oxygen and carbon dioxide are lipophilic molecules which will cross the placenta by simple diffusion. The placental membranes are highly permeable to O(2) and CO(2), thus

blood flow is the rate limiting step for exchange of the respiratory gases across this tissue ***(Carter, 1989).***

2- Glucose transport — Glucose is the primary substrate for fetal oxidative metabolism, the placenta itself is not capable of producing appreciable amounts of glucose until late in gestation ***(Leonce et al., 2006).*** Therefore, uptake of maternal glucose is essential for glycogen synthesis.

Members of the glucose transporter (GLUT) family facilitate glucose transfer, there are 12 members of the GLUT family, however GLUT1 is the only isoform abundantly expressed in early pregnancy and at term, and is the primary placental glucose transporter in humans. There is an asymmetrical distribution of GLUT1 across the placental membrane, with a greater prevalence of GLUT1 on the MVM compared to the BM, suggesting that the rate limiting step of human placental glucose transport may occur at the BM ***(Jones et al., 2007)***. Insulin like growth factor (IGF) 1, a known regulator of fetal growth, increases GLUT1 protein expression and glucose uptake at the BM but not the MVM ***(Baumann et al., 2014)***.

3-Amino acid transport — Amino acids are essential for fetal growth. Transfer involves three fundamental steps: uptake from the maternal circulation across the microvillous membrane, transport through the trophoblast cytoplasm, and transport across the basal membrane into the umbilical circulation**.** Transport systems within the trophoblast can be either sodium-dependent (System A which facilitates the transport of small neutral amino acids such as alanine, serine and glycine into the cell) or sodium-independent (System L which is exchanger for large neutral amino acid transport; it exchanges non-essential amino acids for essential amino acids, such as leucine) and differ based on their ionic substrates**.** All amino acids are not transferred equally and transfer can be impaired in pregnancies complicated by fetal growth restriction ***(Regnault et al., 2005).*** The transport

of amino acids across the BM into fetal circulation occurs via facilitated diffusion down their concentration gradients through the transporters, as well as exchangers ***(Cleal et al., 2011)***.

4-Immunoglobulin G transfer — IgG is transported across the syncytiotrophoblast via the Fc receptor, FcRn ***(Simister, 2003).***

5- Drugs — Most drugs cross the placenta by simple diffusion. Plasma membrane carriers, biotransforming enzymes, and export pumps also play a role ***(Marin et al., 2004).*** Non ionized, non-protein bound, lipid soluble drugs with molecular weight below 600 Daltons freely cross the placenta. High molecular weight drugs, such as insulin (6000 Daltons), are not transported in significant amounts ***(Syme et al., 2004)***.

Protective function: The placenta as a selective barrier

The fetus requires its own unique microenvironment independent of maternal sex or stress hormones and environmental pollutants so that development of its neuroendocrine and gonadal systems is not compromised. Hence, the syncytiotrophoblast is equipped with a variety of enzymes and transporters that ensure the detoxification and efflux of xenobiotic, playing an equivalent role to hepatic cells in the adult. One of the best characterized examples is the enzyme 11-b-hydroxysteroid dehydrogenase 2 (11-bHSD2), which oxidizes maternal cortisol to the inactive metabolite cortisone. In this way, the placenta limits exposure to the potential harmful effects of maternal stress hormones, which when administered direct to the fetus causes reduced cell proliferation and growth restriction ***(Burton and Fowden, 2015 and Dy J et al., 2008)***.

The hypercortisolaemia in the fetal circulation may impact adversely on the development of fetal organ systems, including the brain. It is notable that elevated levels of steroid hormones were recently found in the amniotic fluid of male babies who later developed autism ***(Baron-Cohen et al., 2014)***.

P-glycoprotein and members of the multidrug resistance protein family have been localized to the apical surface of the syncytiotrophoblast and to the endothelium of the villous capillaries at term ***(Burton and Fowden, 2015)***. These transporters mediate the ATP-dependent efflux of a wide range of anionic organic compounds, providing protection to the fetus against exposure to potentially noxious xenobiotic**.** Thus, the placenta forms a barrier to toxins and infective organisms ***(Robbins and Bakardjiev, 2012)***.

Abnormal placentation:

Abnormalities in the process of trophoblastic invasion may result in abnormal placentation. Both the embryonic trophoblast and maternal deciduas produce corticotrophin-releasing hormone (CRH), which promotes implantation. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), which is expressed in extravillous trophoblasts (EVTs) of normal human placenta, may also function in trophoblast/endometrial interactions ***(Bamberger et al., 2006).***

Locally produced CRH plays a role in trophoblast invasion, primarily by regulating CEACAM1 expression. CRH inhibits trophoblast invasion by decreasing the expression of CEACAM1 through an effect that might be involved in the pathophysiology of clinical conditions, such as preeclampsia and placenta accreta ***(Bamberger et al., 2006).***

The hypothalamic neuropeptide corticotrophin releasing hormone (CRH) is produced in several organs of the female reproductive system, including the endometrial glands, decidualized stroma, and trophoblast. In addition, the gene encoding the CRH receptor type 1 (CRHR1) is expressed in human endometrial and myometrial cells, indicating a local effect of uterine CRH. Indeed, locally produced CRH promotes implantation and maintenance of early pregnancy ***(Bamberger et al., 2006).***

The etiology of accreta is due to a deficiency of maternal decidua resulting in placental invasion into the uterine myometrium. The molecular basis for the development of invasive placentation is yet to be elucidated but may involve abnormal paracrine/autocrine signaling between the deficient maternal decidua and the trophoblastic tissue. The interaction of hormones such as Relaxin which is abundant in maternal decidua and insulin-like 4, an insulin-like peptide found in placental trophoblastic tissue may play role in the formation of placenta accreta ***(Goh and Zalud, 2015).***

Anatomy and adaptation of the uterus to pregnancy:

1. **Hypertrophy and dilatation:**

In the non-pregnant woman, the uterus is an almost solid structure weighing about 70 grams with a cavity of 10 milliliter or less. During pregnancy, the uterus is transformed into a relatively thin walled muscular organ of sufficient capacity to accommodate fetus, placenta and amniotic fluid. The average total volume of the contents of the uterus at term about five liters but may be 20 L or more, so that by the end of pregnancy the uterus has achieved a 500 to 1000 times' greater capacity than in the non-pregnant state. There's a corresponding increase in uterine weight, and the body of the uterus at term weighs approximately 1100 g ***(Cunningham, 2001).***

During pregnancy, uterine enlargement involves stretching and marked hypertrophy of existing muscle cells, whereas the appearance of new muscle cells is limited. The myometrial smooth muscle cell is surrounded by an irregular array of collagen fibrils. The force of contraction is transmitted from the contractile proteins of the muscle cell to the surrounding connective tissue through the reticulum of Accompanying the increase in size of the uterine muscle cells during pregnancy, there's an accumulation of fibrous tissue, particularly in the external muscle layer, together with a considerable increase in elastic tissue. The network that is formed adds materially to the strength of the uterine wall. Concomitantly, there's a great increase in size and number of blood vessels and lymphatics. The veins that drain the placental site are transformed into large uterine sinuses, and there's hypertrophy of the nerves exemplified by the increase in size of the frankenhauser cervical ganglion ***(Cunningham, 2001)***.

2. Control of Uteroplacental Blood Flow*:*

The increase in maternal-placental blood flow principally occurs by means of vasodilatation, whereas fetal-placental blood flow is increased by a continuing increase in placental vessels. ***Palmer et al. (1992)*** showed that uterine artery diameter doubled by week 21 and concomitant flow velocity was increased eight folds.

Using measurements of uterine resistance index, ***Juaniaux et al. (1994)*** found that both estradiol and progesterone contributed to the downstream fall in resistance to blood flow with advancing gestational age.

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