



The placenta

Learning module

Developed by Carolyn Hammer

Edited by Fabien Giroux

Diagrams by Dr Yockell –Lelievre where indicated

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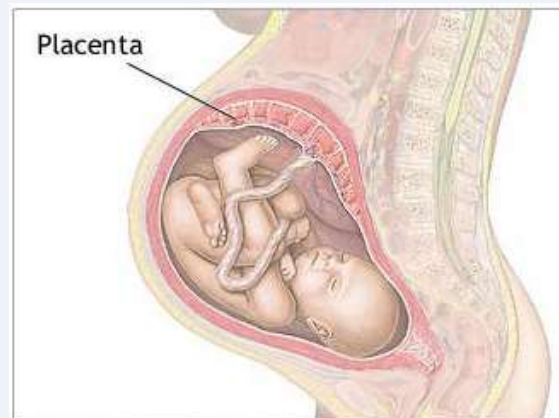
Introduction

What is the placenta?

- The placenta is a:

“vascular (supplied with blood vessels) organ in most mammals that unites the fetus to the uterus of the mother. It mediates the metabolic exchanges of the developing individual through an intimate association of embryonic tissues and of certain uterine tissues, serving the functions of nutrition, respiration, and excretion.” (Online Britannica Encyclopaedia)

- The placenta is also known as a hemochorionic villous organ meaning that the maternal blood comes in contact with the chorion and that villi protrude out of this same structure. As the fetus is growing and developing, it requires a certain amount of gases and nutrients to help support its needs throughout pregnancy. Because the fetus is unable to do so on its own, it is the placenta that carries out this function.



<http://health.allrefer.com/health/placenta-abruptio-placenta.html>

What are the main roles of the placenta?

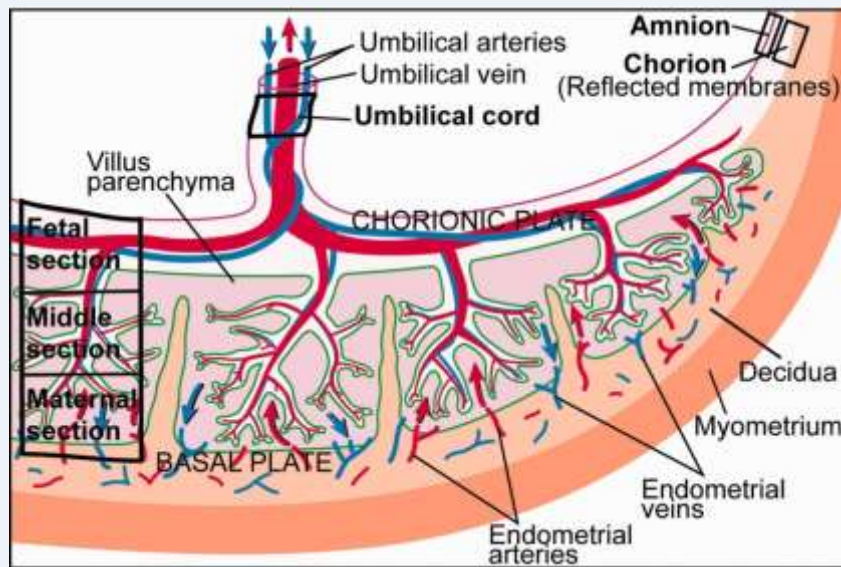
•The placenta provides the connection between fetus and mother in order to help carry out many different functions that it is incapable to do alone. During pregnancy, the placenta has 6 main roles to maintain good health and a good environment for the fetus:

- Respiration
- Nutrition
- Excretion
- Protection
- Endocrine
- Immunity

Anatomy and physiology

Structure

- The placenta is an organ of round or oval shape that is relatively flat. It is about 20 cm in length and has an average weight of 500-600g once at term. These numbers can vary according to the weight of the fetus. It is said that the placenta weighs about one-sixth of that of the fetus.
- The placenta is composed of two different surfaces, the maternal surface, facing towards the outside, and the fetal surface, facing towards the inside, or the fetus. On the fetal surface, there is the umbilical cord, the link between the placenta and the fetus. Components of both of these surfaces will be explained in further detail in the next few slides.



<http://www.pnas.org/content/103/14/5478/F1.expansion.html>



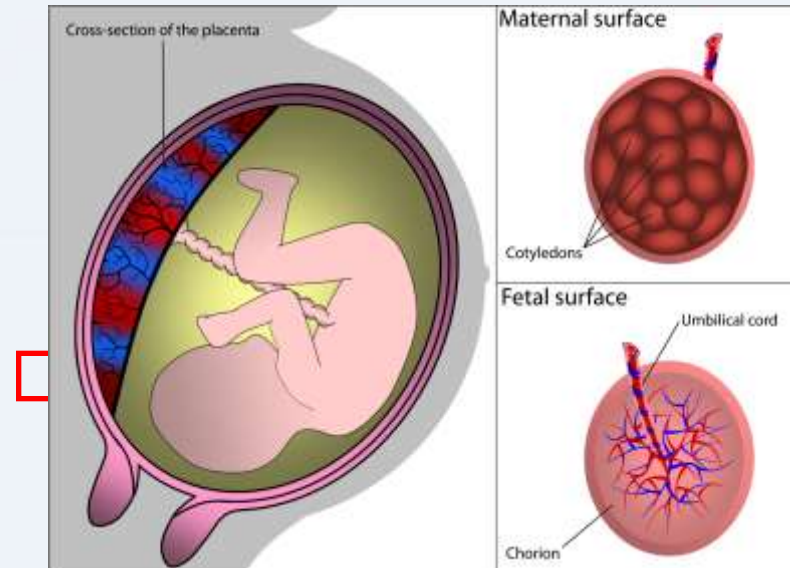
http://homebirthchoices.com/?page_id=95

Fetal surface: Amnion and chorion

- The fetal surface of the placenta is mainly composed of the amnion, chorion and umbilical arteries and veins. This section of the placenta can also be called the chorionic plate.
- The amnion is a clear membranous bag that surrounds the fetus during pregnancy to allow protection. It is avascular and nerveless. Along with surrounding the fetus, the amnion also covers the whole of the umbilical cord. It has a thickness of 0.08-0.12mm and is made up of a single layer of ectodermal epithelium. Both the amnion and chorion begin to develop closely after fertilization until the 28th week of pregnancy. After this week, it is rare that development continues; instead, it will only stretch in size due to the ongoing growth of the fetus inside.
- At about the 3rd week of gestation, the amnion starts to secrete the amniotic fluid. This fluid accumulates in the amniotic cavity pushing the chorion and amnion closer together till they are in close contact during the 7th to 10th week of pregnancy. (We say close contact because there is still a little amount of fluid separating the two membranes called the intermembrane space.) The amniotic fluid is breathed by the fetus and serves as a form of protection and cushion against the walls of the uterus, helps maintain constant pressures and temperatures, allows space for fetal growth and protects against fetal infection.
- The chorion, underlying the amnion is a thicker membrane of about 0.4mm composed of an outer layer of trophoblast cells and a inner layer of somatic mesoderm, the amnion is in close contact to this layer. The chorion is vascular however does not contain any nerves. The blood vessels within the chorion supply the chorion as well as the amnion via passive diffusion.

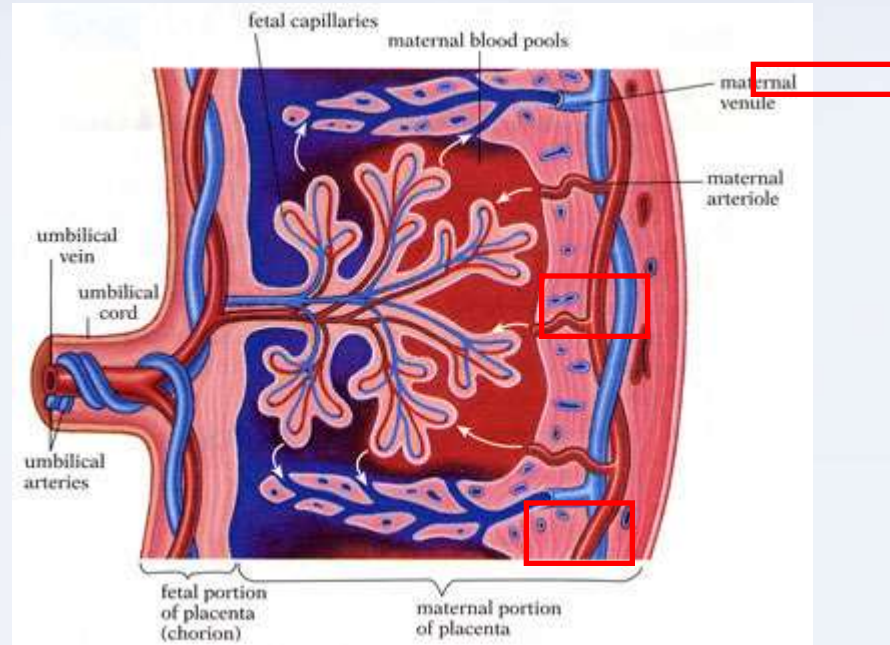
Fetal surface: Amnion and chorion

- The chorion will eventually develop into the chorionic villi where lies a system of fetal capillaries that allow maximum contact area with the maternal blood that is contained in the intervillous space, for gas, nutrient and waste exchange. The development of these villi will be explained in further details in the section *Development and Formation*.
- Also located on the fetal surface of the placenta are the umbilical veins and arteries that are visible through the amnion.



(By Dr. Yockell-Lelievre)

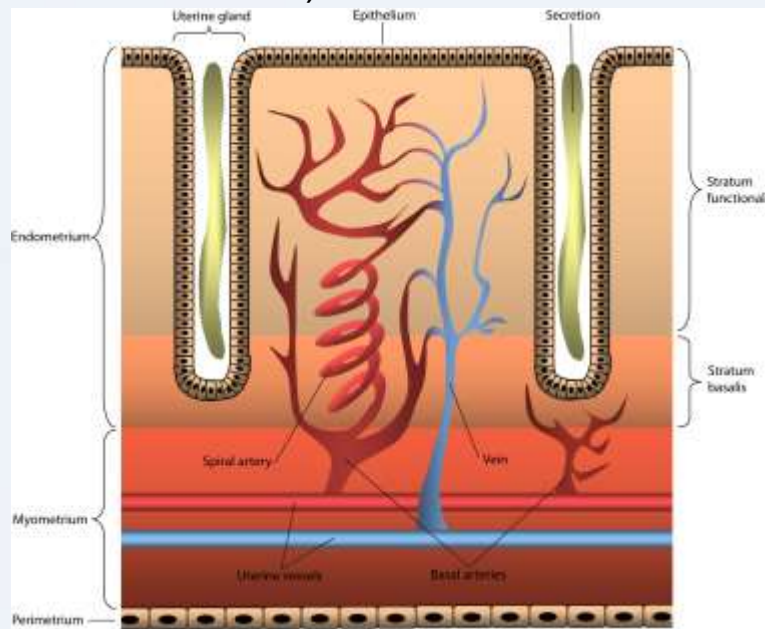
Fetal surface: Amnion and chorion



<http://www.biog1105-1106.org/demos/105/unit8/ovaryplacenta.html>

Maternal surface: Decidua, maternal vessels, intervillous space and cotyledons

- The maternal portion of the placenta is composed of the decidua, the maternal blood vessels, the intervillous space and cotyledons.
- The uterine wall consists of many different layers, the endometrium, the myometrium and the perimetrium (starting from the layer closest to the lumen). The endometrium itself consists of 2 different parts. The section next to the myometrium is the stratum basalis and the section just above (closest to the lumen) is the stratum functionalis.



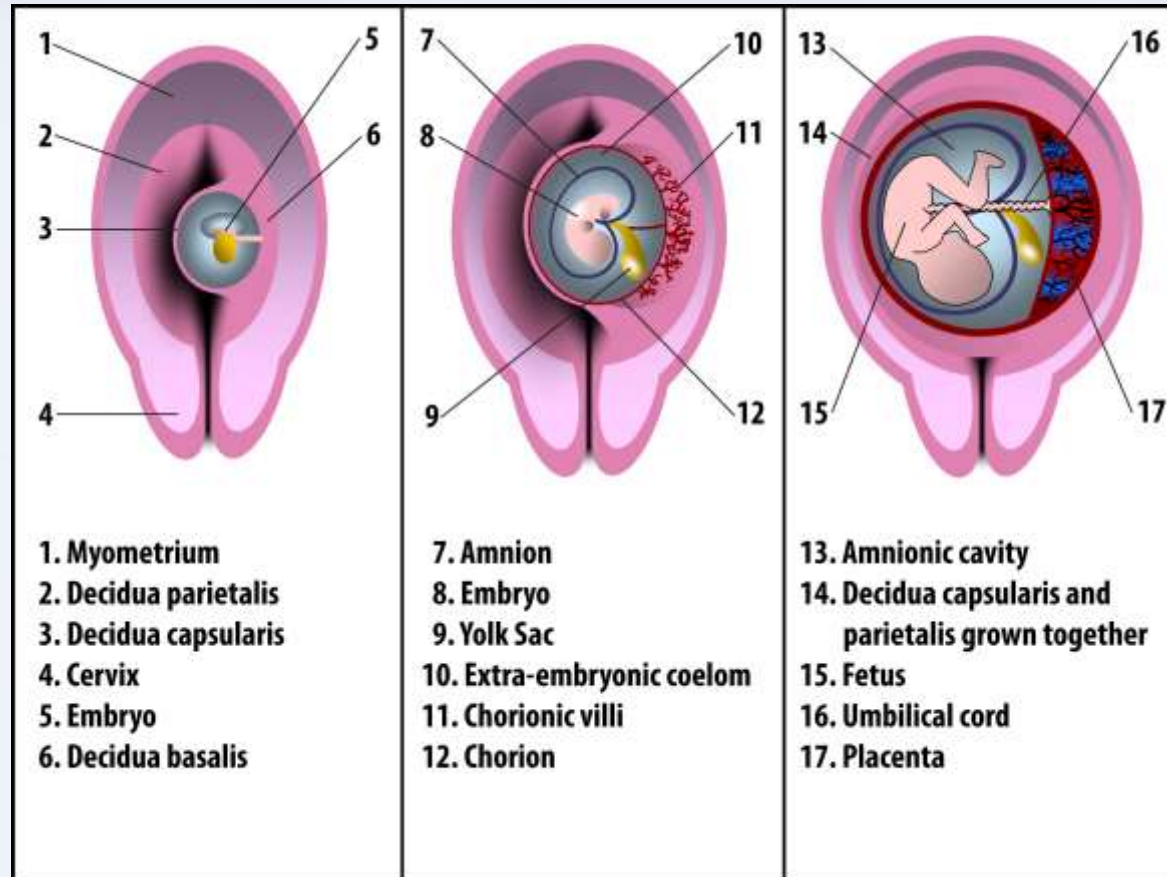
(By Dr. Yockell-Lelievre)

- Once fertilization occurs, a phenomenon called the decidual reaction takes place. The reaction causes changes within the endometrium which causes it to become the decidua.

Maternal surface: Decidua, maternal vessels, intervillous space and cotyledons

- The decidua is what gives the placenta a dark red, blood like appearance on the maternal surface. There are different portions to the decidua that have specific names according to where they are located and what their function is:
 - Decidua capsularis* – This is the section surrounding the chorion. It lies between the uterine wall and the growing fetus.
 - Decidua basalis* – This is the section where implantation takes place and becomes the basal plate also known as the maternal surface of the placenta. It too can be divided into further sections.
 - Decidua parietalis* – This is the section of the decidua lining the rest of the uterus. Near the 12th week of gestation, the decidua parietalis and capsularis come into contact and fuse together.
- In the early development, the decidua plays a role in the nutrition. In addition to this, it will also protect the endometrium and myometrium from further invasion of trophoblast cells during implantation.

Early Placental Development

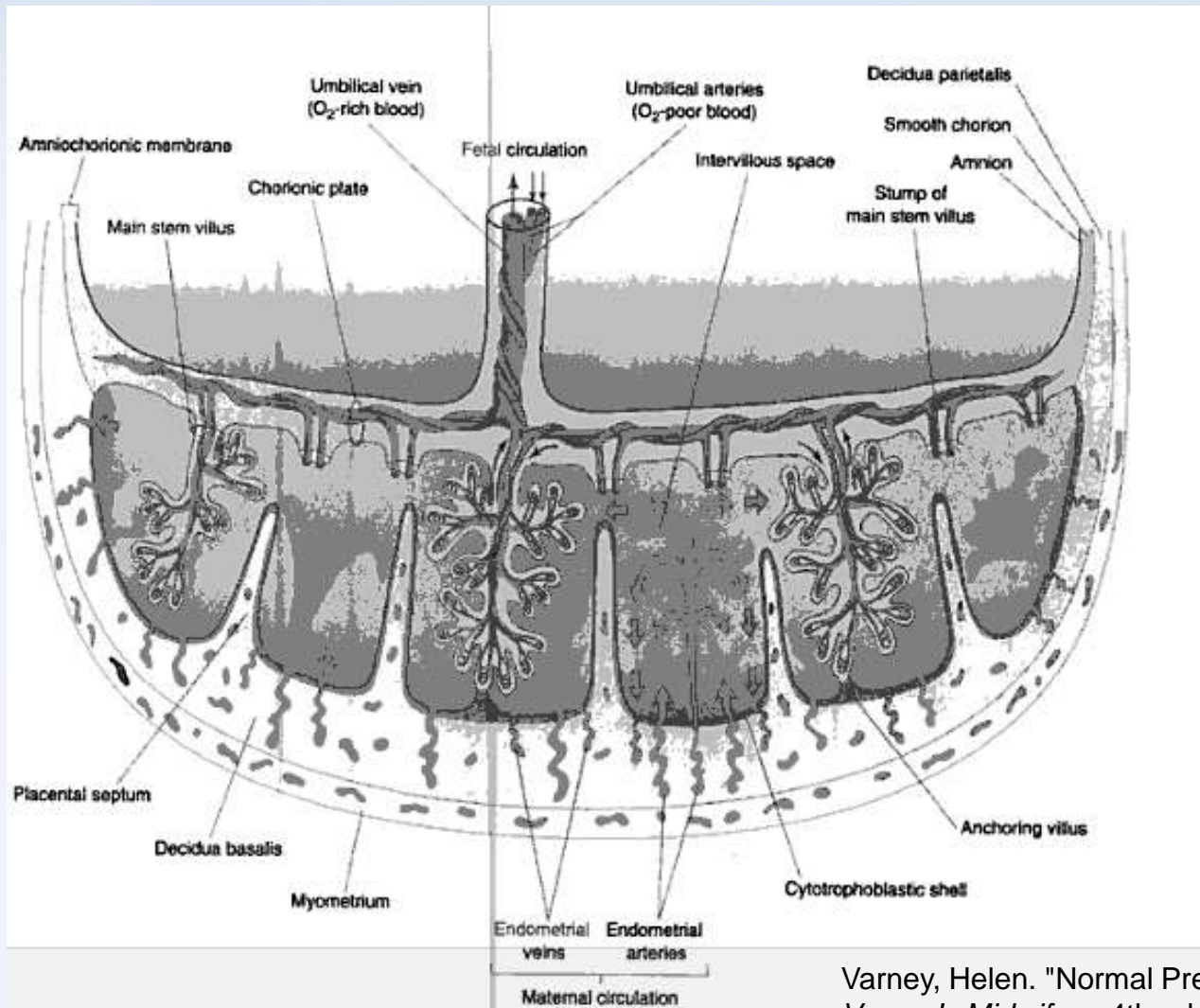


(By Dr. Yockell-Lelievre)

Maternal surface: Decidua, maternal vessels, intervillous space and cotyledons

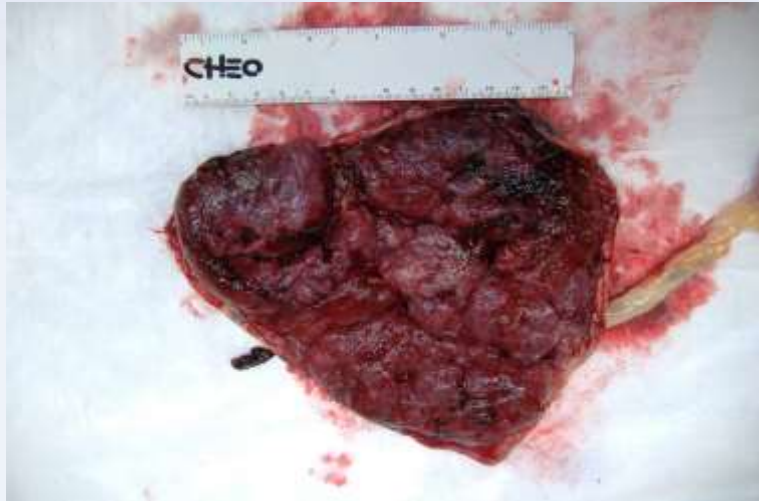
- Also visible on the maternal surface are lobules, approximately 15 to 20 called cotyledons. They are divided by deep channels called the placental septa. Each of these 15-20 cotyledons contain one main stem of a chorionic villi. Each individual lobule is then divided into smaller sections or lobules each containing one chorionic villi. These villi are the same ones emerging from the chorion, containing fetal capillaries, which bathe in the intervillous space (it is important to note that fetal and maternal blood **never** mix).
- Embedded in the decidua are the maternal veins and arteries coming from the uterine wall and terminate in the intervillous space. They are continuous with the maternal circulation. In a non pregnant women, the maternal arteries are spiral arteries. Once pregnancy occurs, these arteries become uteroplacental vessels by the action of the invading trophoblast cells. They become flaccid and saclike and passively dilate in order to better accommodate the greater blood flow to the placenta.
- The intervillous space is simply the space between the mother's blood vessels and the fetal chorionic villi. It is filled with a pool of maternal blood where bathe the villi. This is where all nutrient, gas and waste exchange occur.

Maternal surface: Decidua, maternal vessels, intervillous space and cotyledons

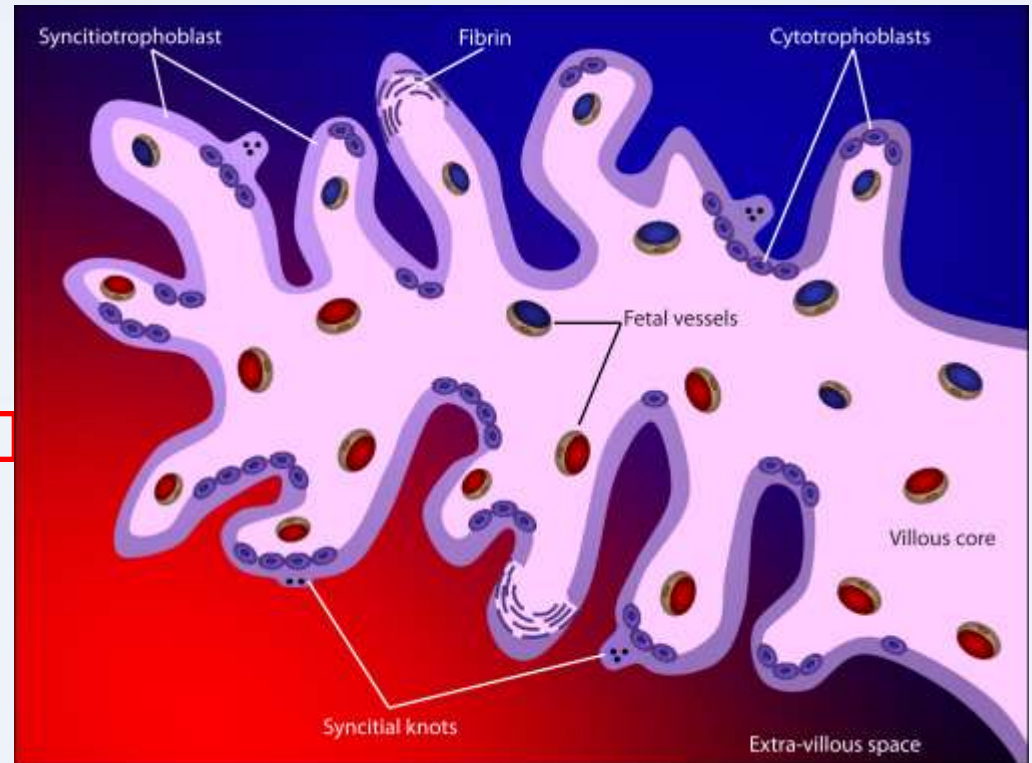


Varney, Helen. "Normal Pregnancy Database." *Varney's Midwifery*. 4th ed. Jones & Bartlett Learning, 2004. 565. *Google Books*.

Maternal surface: Decidua, maternal vessels, intervillous space and cotyledons



Maternal surface of the Placenta

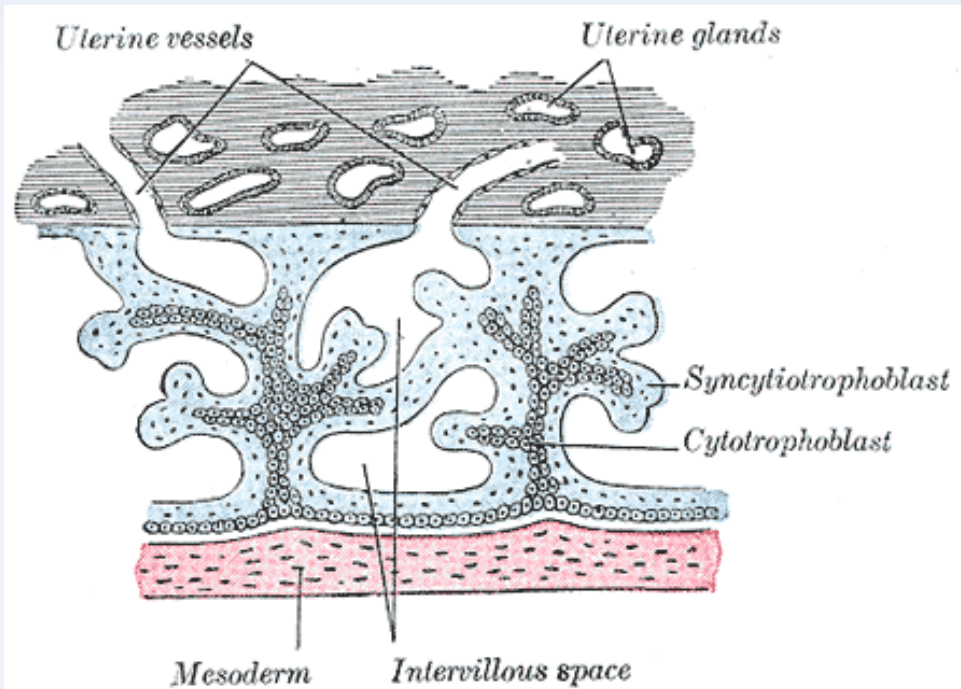


Basic structure of the human villous
By Dr Yockell-Lelievre

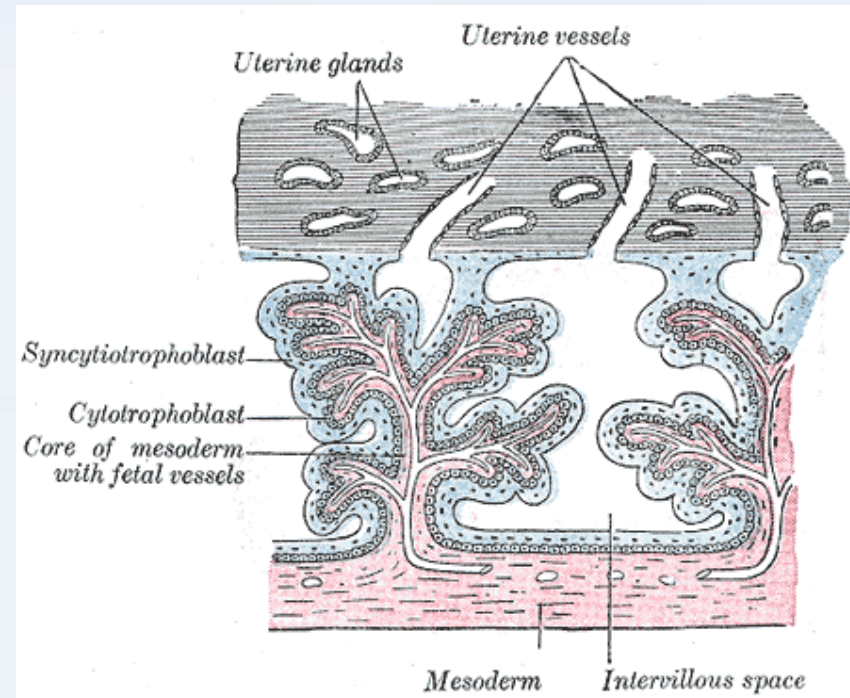
Chorionic villi

- Chorionic villi are one of the most important structures of the placenta. They contain the fetal capillaries and are the recipients of the nutrients and gases coming from the maternal blood in order to nourish the fetus to a healthy growth. Although their appearance change often during the many weeks of pregnancy, their basic structure stays relatively the same. They can be seen as early as the 12th day after fertilization.
- The out layer of the villi is covered by a layer of trophoblastic cells that can be separated into 2 different layers. The outer layer is made up of syncytiotrophoblast and the inner layer is made up of cytotrophoblastic cells also known as Langhans cells. The cytotrophoblast are the stem cells of the trophoblast cells.
- The syncytiotrophoblast cells form a uniform layer around the villi and are in direct contact with the maternal blood, however, both bloods never mix.
- There are different types of villi throughout pregnancy. There are the primary villi, the secondary villi and the tertiary villi or true villi. Their development is later explained.

Chorionic villi



Primary chorionic villi



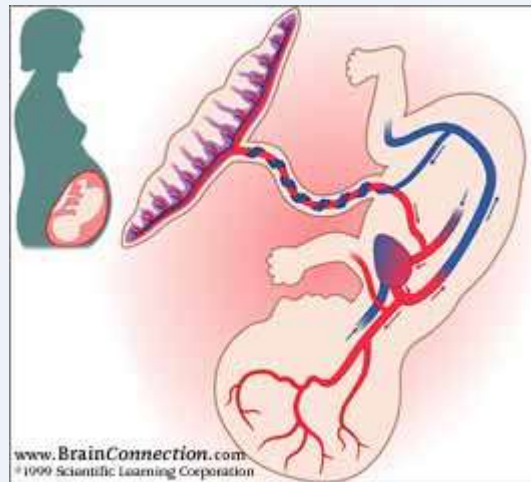
Tertiary chorionic villi

Umbilical cord

- The umbilical cord emerges from the fetal side of the placenta (chorionic plate) to the belly button region of the fetus. At its full length, the cord has an average length of about 50 to 60 cm but can range from 30 to 100 cm with a diameter of 2 to 3 cm. It has a dull white appearance.
- The cord contains 2 arteries and 1 vein that are continuous with the fetal circulation. These vessels are longer than the cord and tend to twist and coil to add strength and protect against entanglement, compression and tension.
- The cord itself is composed of an extracellular matrix known as Wharton's jelly, a specialized connective tissue. This substance helps to protect the vessels within the cord.
- The whole of the umbilical cord is incased by the continuous layer of the amnion that was covering the fetal surface of the placenta.

Placental circulation

- Placental circulation encompasses two different circulation systems, the maternal and the fetal. Although these two come in very close contact with each other, they will never mix together, they are separated by what is known as the placental barrier. This organisation keeps the mother's body from rejecting the fetus as an object of foreign origin.
- These two independent blood flows can be influenced by different factors such as blood pressure, medication, uterine contractions, hormones, etc.
- It is the nutrients, gases, wastes and hormones that flow through these circulations which can then switch systems (fetal to maternal or vice versa) by diffusion. The site where this exchange occurs is determined by the fetal membrane which includes the trophoblast (more specifically the syncytiotrophoblast), the chorionic villi and the fetal capillaries.

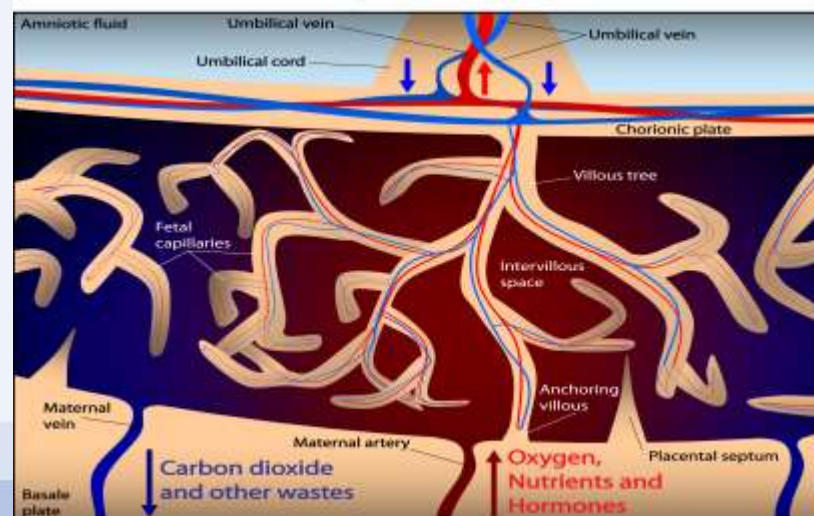


<http://brainconnection.positscience.com/topics/?main=gal/fetal-circulation>

Placental circulation

Fetal circulation

- This circulation system takes place in the fetus, umbilical cord and villi located in the placenta.
- Deoxygenated blood from the fetus goes through the two umbilical arteries into the placenta, therefore, each artery can supply blood to half of the placenta. Where the umbilical vessels reach the placenta, they branch out under the amnion into what is called the chorionic vessels. Take note that the arteries always cross over veins. High oxygen content blood will return to the fetus via the umbilical vein.
- The chorionic vessels further divide into the different villi to form the fetal capillaries. As the blood enters the villi, they each supply one cotyledon. In this section, waste and carbon dioxide (CO₂) are eliminated from the fetus by diffusing into the maternal circulation and leave the placenta by the maternal veins.



(By Dr Yockell-Lelievre)

Placental circulation

Maternal circulation

- Maternal circulation is also called uteroplacental circulation. This takes place in the mother and the intervillous space of the placenta. This circulation is constantly changing to meet the needs of the growing fetus.
- Oxygenated blood arriving from the mother's endometrium enters the placenta through the maternal spiral arteries which pool into the intervillous space. Unlike the fetal vessels that supply a specific part of the placenta, the maternal veins and arteries are randomly placed.
- It is the maternal blood pressure that drives blood into the intervillous space. The blood will then flow around the villi allowing oxygen, nutrients and hormones to diffuse into the villi, into the fetal capillaries, where they are then delivered to the baby via the umbilical vein. This process is slow to allow maximum transfer. Deoxygenated blood will then flow out of the intervillous space by the uterine veins back into the mother's circulation.

Placental circulation

- Here in a short video to clarify some of the concepts previously discussed:
<http://www.youtube.com/watch?v=jQzRkbBNIYA>

Roles and functions

Roles and functions

- The placenta has many different roles and functions throughout pregnancy. It is important for the exchange of oxygen and carbon dioxide, the elimination of wastes, the transfer of nutrients, the synthesis of certain hormones, protection and immunity. With the said, the placenta has essentially 4 main roles:
 - Metabolic
 - Endocrine
 - Transport
 - Immunologic
- Most of the placenta's substances involved in the different functions undergo some sort of transfer in order to move from the fetus to the mother and vice versa. This transfer occurs in the syncytiotrophoblast cells composing the villous where substances move from the apical membrane (next to the maternal blood) to the basal membrane (next to the fetal capillaries). All the substances will be transferred by different mechanisms, including passive diffusion, facilitated diffusion, active transport, endocytosis, exocytosis, etc. Transporters located on both sides of the syncytiotrophoblast help in these transfer processes.

Respiration

- Early in pregnancy, the fetus does not have adequately developed lungs to breathe on its own, therefore, one of the main functions of the placenta is to help the fetus breathe. It is only after delivery that the child can breathe with its own lungs.
- When we breathe, we inhale oxygen and exhale carbon dioxide. This is the same principle with the fetus. Oxygen-rich blood coming from the mother enters the placenta by the maternal artery and pools in the intervillous space. Oxygen uses mostly simple diffusion to enter the fetal capillaries and is helped by a relatively high pressure gradient between the two compartments on either side of the membrane because of its higher difficulty to diffuse. Oxygen will also occasionally transfer across the placenta by facilitated diffusion. Once inside the fetal capillaries, the oxygen will travel along the umbilical vein where it will reach the fetus.
- On the other hand, the fetus produces much more carbon dioxide than the mother, which needs to be eliminated. The carbon dioxide will thus make its way through the umbilical arteries to the placenta and use diffusion to cross from the villi into the intervillous space. Carbon dioxide is very soluble and therefore can diffuse very easily. Once in the intervillous space, the gas is added to the maternal circulation where it is eliminated by the mother's lungs.
- The rate at which this gas exchange will occur depends on the amount of blood flow from the maternal circulation that supplies these gases to the placenta.



Nutrition and excretion

- A good supply of nutrients for the fetus is needed for energy and a healthy growth. Nutrients such as glucose, amino acids and fatty acids are essential to life and are mostly found in the foods we eat. Because the fetus is not physically eating, it is the mother that supplies these nutrients via the placenta. Glucose is the most important nutrient for fetal life and since the fetus is unable of gluconeogenesis due to reduced oxygen levels, the mothers nutrition is of utmost importance.
- Different foods that the mother eats are broken down and transported by the blood to the uterine wall. These nutrients found in the maternal circulation are absorbed by the placenta and can be broken down into smaller particles to facilitate the uptake of these molecules by fetal cells. Some of these nutrients, such as glucose, can also be stored or synthesized by the placenta and used later on when they are needed. The placenta is therefore essential to the life of the fetus.
- The mechanism by which these nutrients are absorbed into the fetal circulation is by passive diffusion, facilitated diffusion and active transport.
 - Glucose is transported into the placenta by facilitated diffusion, using the protein carriers GLUT1 and GLUT3. The mechanism is not quite known yet, however, it is said that it resembles the process found in red blood cells. The flow of glucose is also dependent of its concentration on either side of the trophoblast cells.

Nutrition and excretion

- Amino acids are transported into the placenta by active transport because of higher concentrations found in the fetus compared to the mother. This process uses energy dependant carriers to move substances against their concentration gradient. The carriers involved in this process can transport different amino acids that have similar structures therefore a certain amino acid can be transported by different carriers. In addition, because the amount of amino acids being transported into the fetus is much higher then needed, it is believed that the baby uses some of these for energy and to produce other amino acids.
- Fatty acids are transported into the placenta by passive diffusion. The placenta is composed of cells that have a high lipid content in their cell walls, therefore, fatty acids can easily pass through this membrane to enter the fetal circulation.

• When we eat, we also produce waste that is eventually excreted. The fetus also produces waste which needs to be eliminated. These fetal wastes such as urea, creatinine and uric acid cross over into the maternal circulation via simple diffusion to be eventually excreted by the mother.



Protection and immunity

- The placenta is a very important form of protection. One of its functions is to prevent the mothers body of rejecting the fetus. Because the two can have different chromosomes and blood types, the mother would perceive the fetus as an object of foreign origin and would want to reject it because it is not part of her own tissues. However, this scenario does not happen because the placenta serves as a barrier to prevent the two different circulation from mixing therefore the mothers immune system will not attack the fetus.
- The placenta also plays a role as a protective barrier against bacteria. Most bacteria are too big to cross into the fetal circulation, however, micro-organisms such as viruses can do so and infect the fetus. Drugs can also cross the barrier and cause harm to the baby. Drugs such as acetaminophen are harmless however others such as warfarin are dangerous to the growing fetus.
- The placenta can also allow certain maternal protective antibodies, immunoglobulin G class, to cross into the fetal circulation and help protect the fetus from dangerous organisms which can last up to several month after birth. (It is important to consider that not all antibodies are protective and some can be dangerous and cause harm to the fetus.)

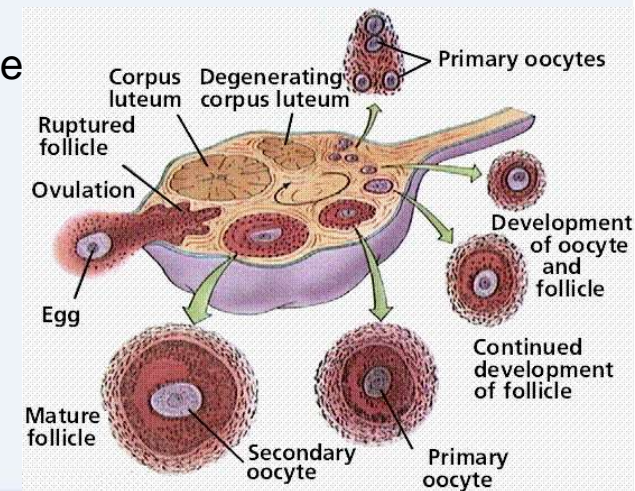


Endocrine

- An other main function of the placenta is acting as an endocrine gland, a gland that secretes hormones directly into the blood. This organ secretes many different hormones into the blood stream to support pregnancy and fetal growth.
- The 4 main hormones produced by the placenta are human chorionic gonadotropin (hCG), human placental lactogen (hPL), estrogens and progesterone. They all play a different role and have specific functions during pregnancy.

A few things to know

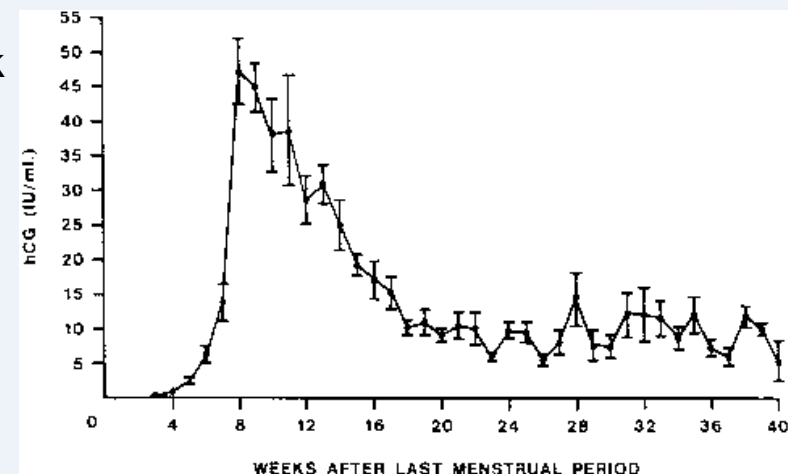
- The corpus luteum is what is left of the follicle once the mother has ovulated. It is maintained by hCG once pregnancy has taken place. It produces mostly progesterone and little estrogen which helps to thicken the uterine wall for the implantation of the fertilized egg and will continue to produce this hormone until the placenta can take over. The corpus luteum is also important to maintain a healthy pregnancy. If no pregnancy were to occur, no hCG would be produced therefore the corpus luteum would start to regress and lead to menstruation.



Endocrine

1) Human chorionic gonadotropin (hCG)

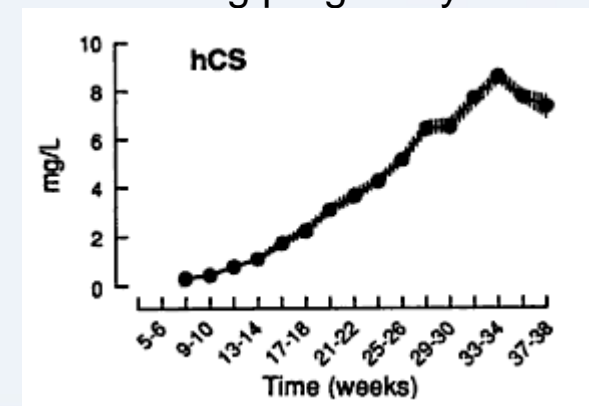
- When taking a pregnancy test, it is the level of hCG, detected in the urine that will give the result of being pregnant. This can be detected at about 3 weeks after fertilization.
- The placenta starts the production of hCG after implantation has occurred. It is produced by the syncytiotrophoblast cells of the chorionic villi and is secreted into the intervillous space. The main and essential role of hCG is the maintaining of the corpus luteum during the early stages of pregnancy therefore maintaining adequate levels of progesterone until the placenta can take over. This hormone may also have a role in the stimulation of the fetal testes and adrenal gland in order to amplify the secretion of testosterone and other corticosteroid as well as stimulation of the production of placental progesterone and diminish the maternal lymphocyte response. This last function can help in preventing the rejection of the fetus by the mothers body. Once the placenta is able to produce the right amount of progesterone on its own, at about the 8th week of pregnancy, hCG levels drop and stay relatively low. About 2 weeks after pregnancy, concentrations of hCG are non-existent.



Endocrine

2) Human placental lactogen (hPL)

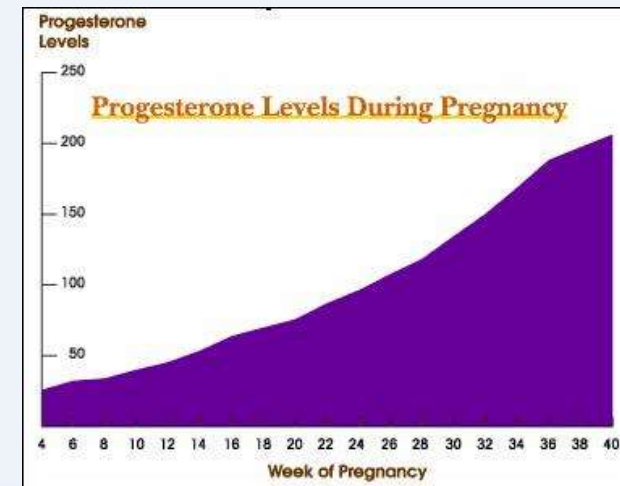
- Human placental lactogen, hPL, is also known as hCS, human chorionic somatomammotropin. It is also produced by the syncytiotrophoblast and at a constant growing rate, produced in small quantities at the beginning of pregnancy and reaching a peak near the end of gestation. Production begins at about 5 -10 days after fertilization and rises. With this said, there is a good correlation between hPL and placental weight. This also makes hPL the most abundant of all secretions done by the placenta.
- This hormone has 2 important functions in the mother, increasing lipolysis and decreasing glucose uptake and gluconeogenesis. These functions in the mother help fetal growth by increasing the amount of glucose and amino acids available for the fetus. hPL has also been found to act as an insulin antagonist. This will increase the mother's metabolism for fats as a form of energy to reduce her uptake of glucose. This will also allow an increase in glucose available for the fetus. Therefore, hPL acts similarly to a growth hormone during pregnancy.
- The secretion of this hormone is mostly regulated by glucose itself. When glucose levels are low, hPL will be secreted which will also lead to an increase in lipolysis.



Endocrine

3) Progesterone

- Progesterone is produced by the corpus luteum during early pregnancy, which is stimulated by levels of hCG, until the placenta can take over (at about 6-8 weeks of gestation). This hormone plays several different roles throughout pregnancy while its secretion constantly rises until birth of the baby.
- Progesterone plays an important part in decreasing the myometrial activity by affecting the uterine smooth muscles. The myometrium is a layer in the uterine wall composed of smooth muscle that can contract and relax. Therefore, this hormone decreases uterine contractions to allow for better implantation and growth. This is done by inhibiting the secretion of prostaglandins, a molecule that regulates the contraction and relaxation of smooth muscle.
- An other role that progesterone plays is to maintain pregnancy by decreasing the immunologic response of the mother's body towards the baby, thus, preventing the rejection of the fetus. This is done by inhibiting T-lymphocyte-mediated processes that play a role in the rejection of tissues.
- Because the fetus lacks certain enzymes, progesterone is also important for the fetus by acting as a substrate for the production of different adrenal gland products such as mineralocorticoids and glucocorticoids. Thus, the fetus must use this placental progesterone in order to accomplish synthesis of these molecules.

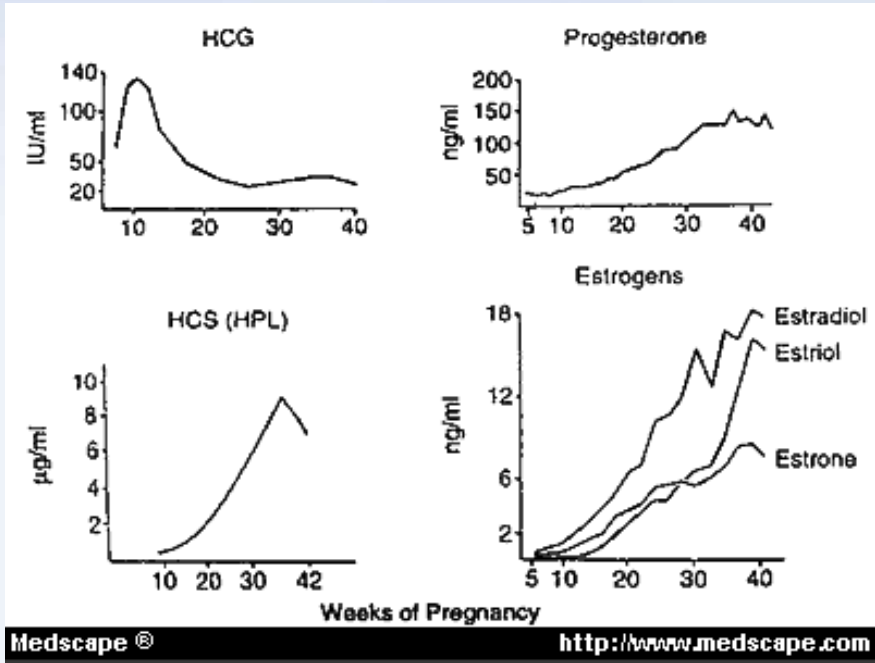


Endocrine

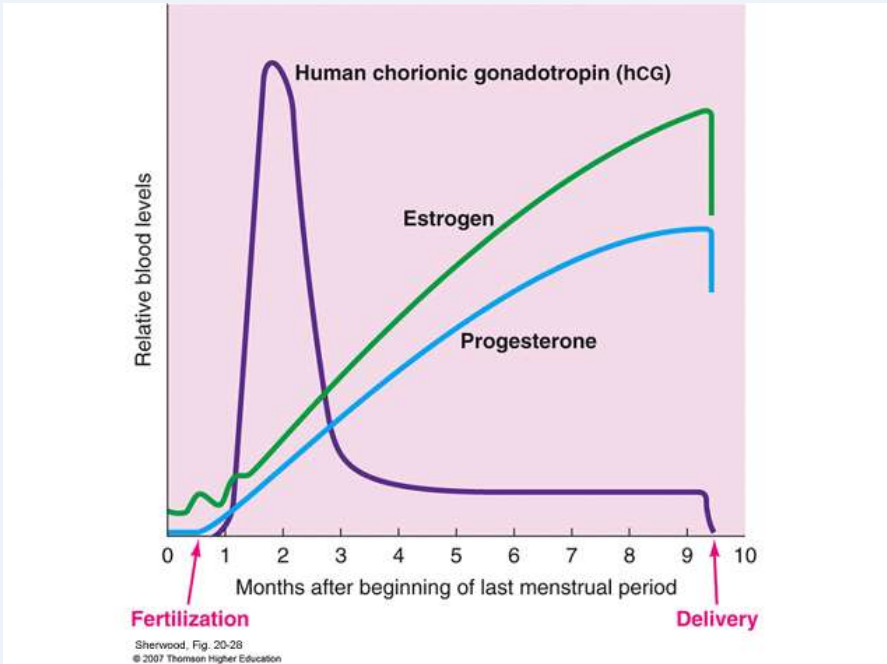
4) Estrogens

- It is important to note that there are many 3 main types of estrogens, estrone, estradiol and estriol, estriol being the most important and abundant estrogen produced during pregnancy. Estrogen is also produced by the corpus luteum before the placenta can take over. Its secretion also rises constantly during pregnancy and plays different roles throughout this time.
- This hormone plays a major role in child birth (parturition) and determining when the time is right for labour. This hormone has different functions such as increasing prostaglandin production and increasing myometrial activity in order to determine the time of labour. An other important function of estrogen, estriol to be more exact, is to increase blood flow to the fetus which in turn will increase the amount of oxygen and nutrient available to it.
- An other role played by estrogen is to increase the secretion of prolactin. Prolactin stimulates the mammary glands to produce milk during pregnancy. It is only near the end of the 9 months that milk production will start, that is when progesterone levels drop. In other words, estrogen prepares the breast for lactation. In addition, estrogen plays a role on other endocrine systems such as the renin-angiotensin system and can help in the development of the fetus as well as maturation of organs.

Endocrine



http://www.medscape.com/viewarticle/408910_2



<http://www.colorado.edu/intphys/Class/IPHY3430-200/image/figure2028.jpg>

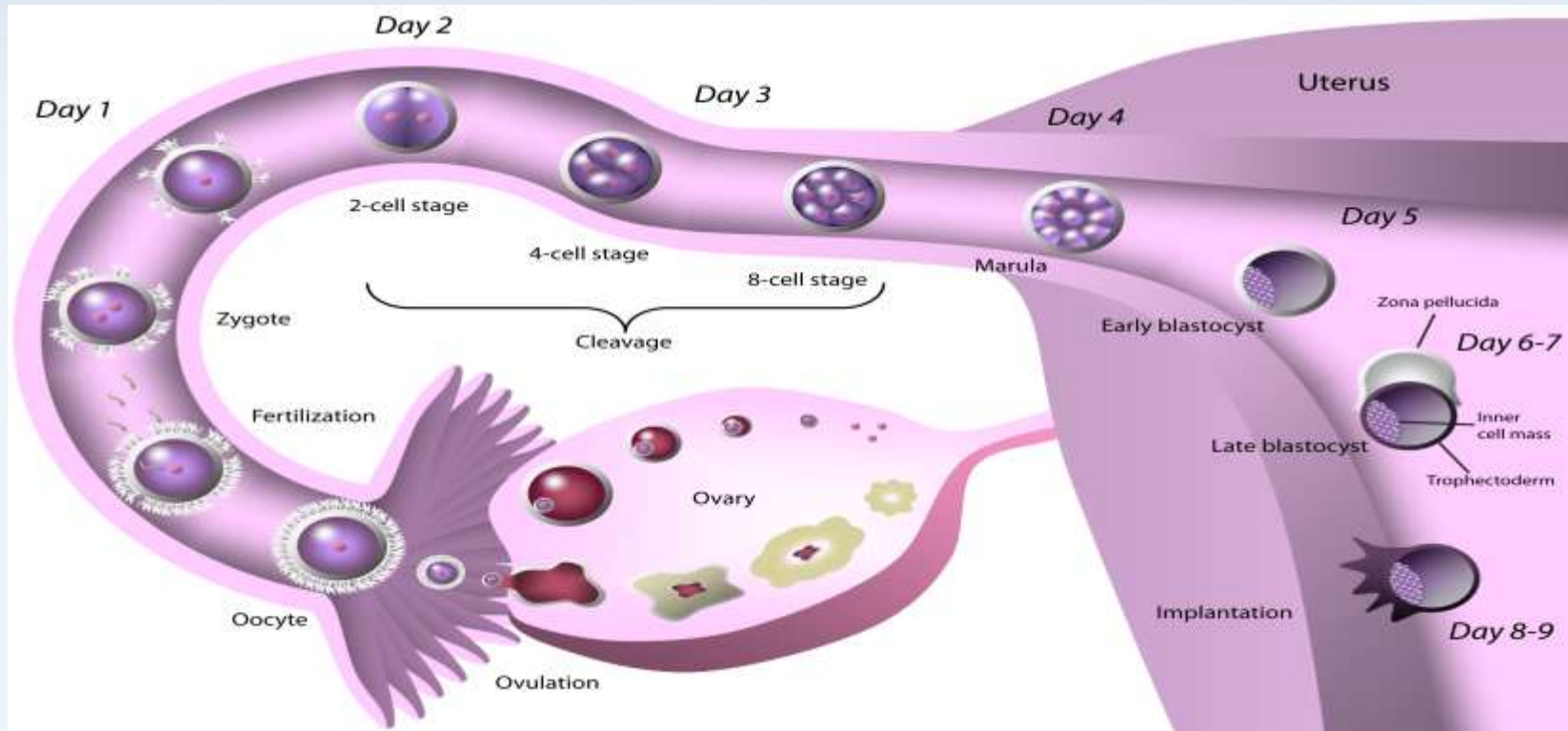
Development and formation

Stages of development

In order to explain and understand the development and formation of the placenta, it is important to know what happens before in order to get to that stage of the pregnancy. Listed below is a brief description of the different stages during pregnancy:

- First off there is ovulation. Ovulation is when the egg leaves the ovary to make its way through the fallopian tubes in order to be fertilized. Day 0.
- Next, there is fertilization. Fertilization is when there is the fusion of a spermatozoid with the ovulated egg to begin the formation a zygote. Day 1.
- In the next few days, this newly fertilized egg completes many cell divisions in the fallopian tube to end up with a total of 32 cells. All these cells are known as totipotent, which means that they can each become an individual. Day 2-4.
- Once the zygote reaches the uterus the cell divisions continue and the zygote becomes a blastocyst. At this stage, the cells are no longer totipotent and begin to differentiate into either the developing baby, or the placenta. Day 5.
- The next step is implantation. Implantation is known as the stage where the blastocyst embeds itself in the endometrium, the inner membrane of the uterus. This usually occurs near the top of the uterus and on the posterior wall. Day 6-8.
- The process of implantation is complete at about 9-10 days after ovulation.

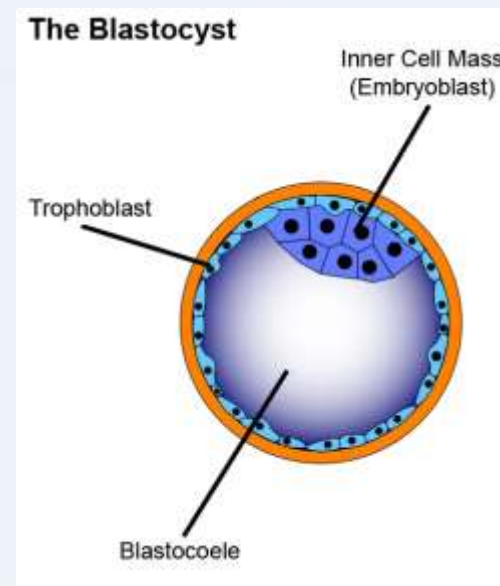
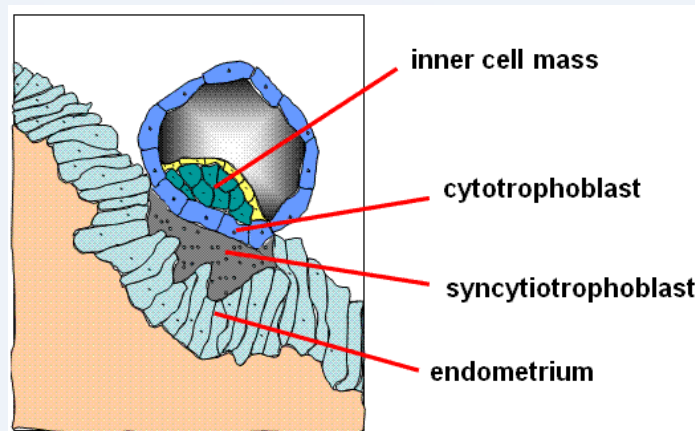
Stages of development



By Dr Yockell-Lelievre

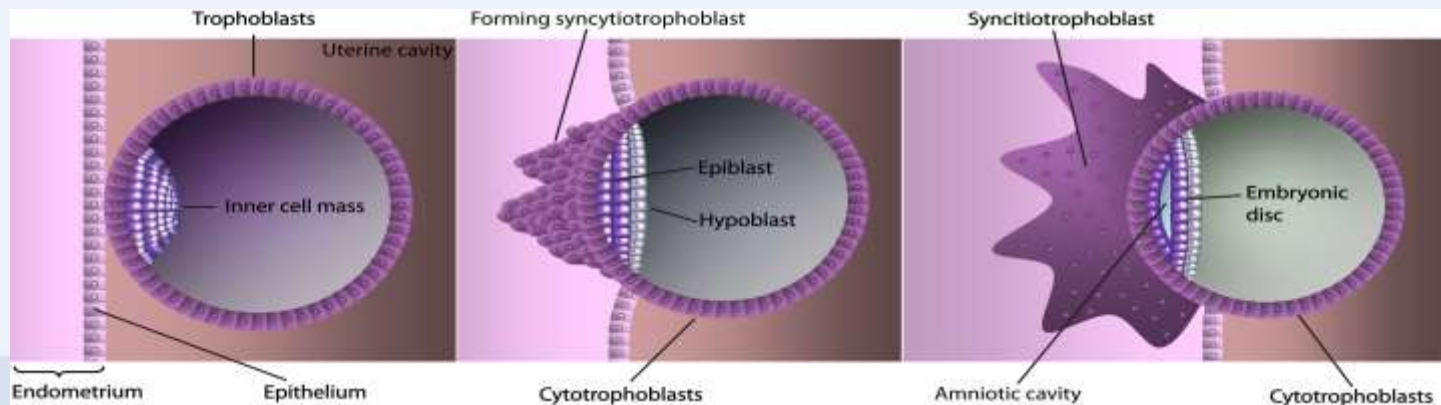
Development of the placenta

- The formation of the placenta begins at the blastocyst stage, when implantation starts to occur. At this stage, it was mentioned that the cells are no longer totipotent and have begun to differentiate. There are 2 different types of cells that are found, the trophoblast cells and the inner cell mass.
- The trophoblast is the layer of cells that make up the surrounding wall of the blastocyst that will become the placenta as well as other membranes. The inner cell mass is an aggregation of cells that will eventually become the growing fetus. In addition, at about the 7th day after fertilization the trophoblast cells further divided into the cytotrophoblast, inner layer, and the syncytiotrophoblast cells, outer layer, (cytotrophoblast give rise to the syncytiotrophoblast).



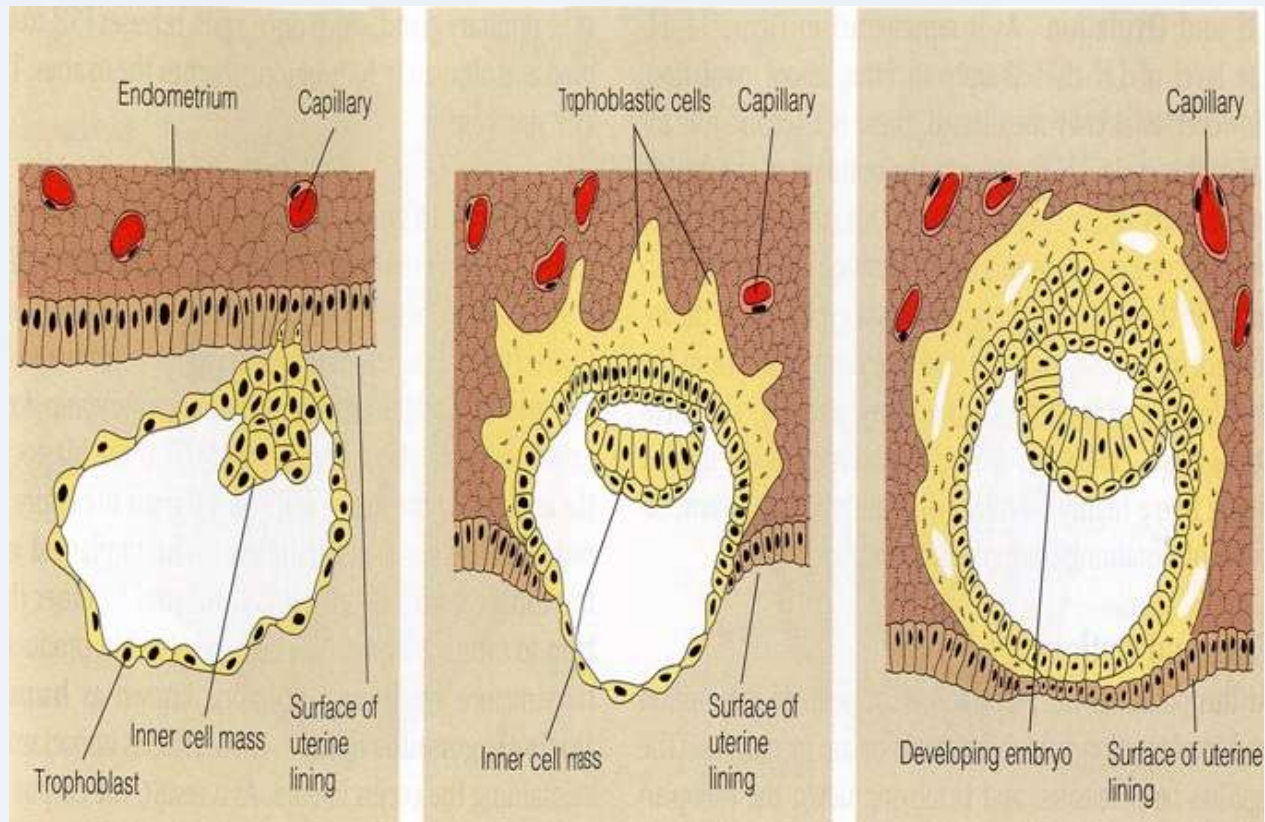
Development of the placenta

- After fertilization, the uterine wall is also going through some changes, preparing to accept the developing blastocyst. Because of the actions of progesterone and estrogens, the cells of uterine wall will increase in size, hypertrophy, and will develop subnuclear vacuoles that are rich in glycogen and lipids. These vacuoles containing glycogen and lipids are the main source of nutrients for the blastocyst which gives rise to implantation.
- Once the blastocyst reaches the uterine wall, the syncytiotrophoblast cells, containing finger like projections, start invading the decidua by eating away at the cells making up the uterine wall. This stage is characterized by a rapid cell division of the trophoblast to make sure that the blastocyst can full embed itself in the decidua. The erosion of the endometrium gives rise to intervillous space that will soon be filled with maternal blood caused by invasion of maternal arteries in this region.
- On the fetal side, the cytotrophoblast cells are very active and will eventually give rise to the chorionic villi where all the nutrient, gas and waste exchange occurs without the mixing of blood.



Development of the placenta

- Eventually, the blastocyst is entirely covered by cells of the uterine wall. This completes implantation. It is important to keep in mind that during the whole process of development, the fetal cells are always separated from the mothers uterine cells and blood. This separation is accomplished by the trophoblast.

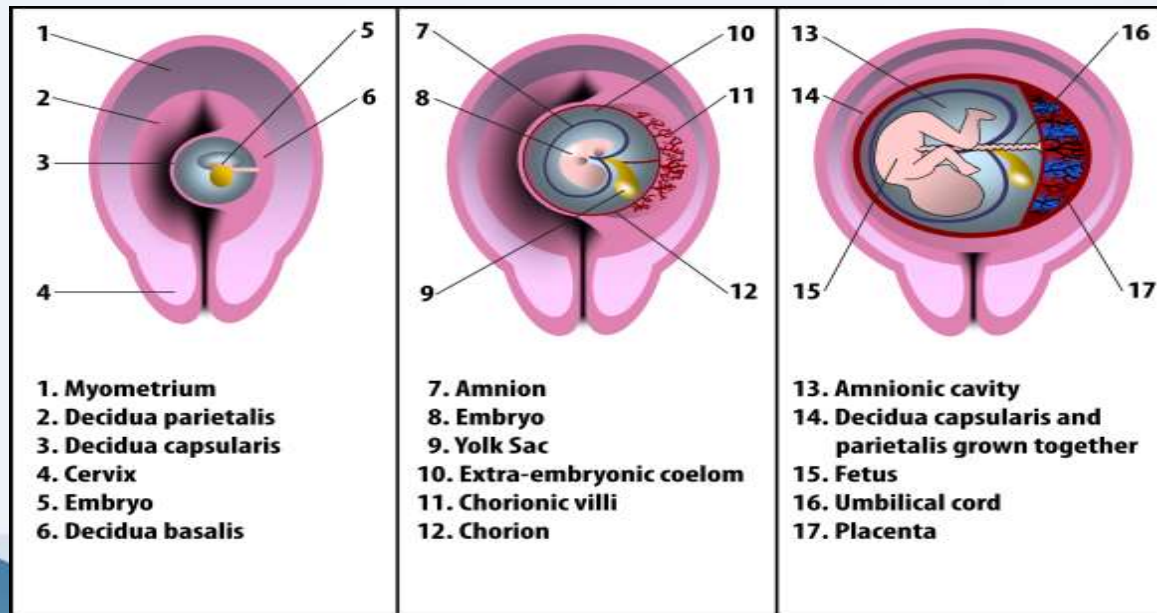


Development of the placenta

- One of the most important structures of the placenta are the chorionic villi which are derived by the cytotrophoblastic cells. As these cells are dividing and enlarging, lacunae, or gaps, start to appear forming columns of cytotrophoblast cells, these are known as the primary chorionic villi.
- Within these primary villi, a mesenchymal core starts to grow, a type of stem cell or connective tissue that is not differentiated, forming the secondary chorionic villi. Once the mesenchymal core differentiates into blood vessels, we now obtain tertiary chorionic villi that will eventually become the terminal villous tree.
- The columns of cytotrophoblastic cells continue to divide and start proliferating through the syncytiotrophoblast and also start projecting towards each other. Eventually, the ends of the villi, formed mostly of cytotrophoblast cells, reach the decidua and the intervillous spaces become distinct.
- At this stage, the mature structure of the placenta is well established. At about the end of the 4th month of pregnancy, the placenta does not undergo any further modification and will only keep growing as well as increase the number of branching of the villous tree until delivery.

Development of the placenta

- Finally, the last thing that should be mentioned is the development of the amnion, the membrane that covers the fetal part of the placenta.
- Cells forming the amnion are derived by the outer layer of the inner cell mass, not from the trophoblast cells like most structures of the placenta. With this said, in the early stages of development, the amnion is in direct contact with the embryo until about the 4th to 5th week of gestation. After this point, fluid starts to accumulate between the embryo and the membrane creating what is known the amniotic cavity. This fluid is the amniotic fluid which has many different functions earlier described in this presentation.
- After a few more weeks, while the fetus is growing, the amnion will fuse with the chorion to form one combined external membrane that will envelop the fetus.



By Dr Yockell-Lelievre

Development of the placenta

•For more information, here are a few videos that can help clarify certain concepts previously mentioned and give you a better general idea on the development of the placenta:

- http://www.youtube.com/watch?v=J_knnENhzwg&feature=related
- <http://www.youtube.com/watch?v=jQzRkbBNIYA> (0:00-4:15min)



www.pregnancydiary.net/

What happens after birth?

After birth

- With the help of the contraction and relaxation movement of the uterus during labour, the placenta detaches itself from the uterine wall. Following this, the placenta will naturally come out on its own about 15-30 minutes after the birth of the baby. The injection of oxytocin can also stimulate the separation of the placenta by stimulating contractions.
- Once the baby is born, placentae are brought to pathology where they are examined. Any mother who had a high risk pregnancy or any complications during her pregnancy will have their placenta thoroughly examined. A number of important pathological processes can then be elucidated and the information used for the management of subsequent pregnancies.



What happens when things go wrong?

Placental pathologies

- Studies reveal that placental pathologies explain almost 25% of stillbirths for example and that placental histology is the most likely source of positive information in the investigation of stillbirth (JAMA 2011, Dec 14, 306 (22): 2459-68)
- Placental-mediated diseases include a variety of conditions, most importantly preeclampsia (early-onset i.e. prior to 34 weeks) and Fetal Growth Restriction.



www.medicexchange.com/Ultrasound/

Placental pathologies -Pre Eclampsia (PE): Definition PE

CLASSIFICATION : Hypertensive Disorders in Pregnancy Recommendations

1. Hypertensive disorders of pregnancy should be classified as pre-existing or gestational hypertension on the basis of different diagnostic and therapeutic factors.
2. The presence or absence of preeclampsia must be ascertained given its clear association with more adverse maternal and perinatal outcomes.
3. In women with pre-existing hypertension, preeclampsia should be defined as resistant hypertension, new *or* worsening proteinuria, *or* one or more of the other adverse conditions.
4. In women with gestational hypertension, preeclampsia should be defined as new-onset proteinuria *or* one or more of the other adverse conditions.
5. Severe preeclampsia should be defined as preeclampsia with onset before 34 weeks' gestation, with heavy proteinuria or with one or more adverse conditions.
6. The term PIH (pregnancy-induced hypertension) should be abandoned, as its meaning in clinical practice is unclear.

(Diagnosis, Evaluation and Management Hypertensive Disorders of Pregnancy: JOGC March 2008)

PE: early and late onset diseases

Apples and Oranges

- PE can be divided into two major categories; early and late onset diseases.
- Early onset PE refers to the occurrence of PE prior to 34 weeks. It is usually associated with major fetal/neonatal/maternal morbidity and mortality and specific placental pathology.
- Late onset disease is more commonly associated with adequate placentation in the context of excessive fetal demands, as in fetal macrosomia and multiple gestations
- The literature supports the concept that early and late onset diseases have different etiologies.

Possible Etiology Early Onset Preeclampsia (PE)

- Although the clinical symptoms of PE are not recognized before 20 weeks gestation, it is truly a first trimester pathology.
- In early placentation, undifferentiated cytotrophoblasts invade the maternal interface and assist in the transformation of spiral arteries from high resistance, low capacitance vessels into low resistance and higher capacitance structures which will help supply the growing fetus and placenta.
- This occurs through the replacement of arterial endothelial cells surrounding these spiral arteries by endovascular trophoblasts derived from these invasive trophoblasts.
- Women with PE show inadequate transformation of their spiral arteries. This is thought to result in the development of hypoxia and hypoxia-regeneration insults with oxidative stress. These phenomena lead to maternal endothelial cell activation through the release of “debris” from the placenta and the production of anti angiogenic factors such as s-Flt and s-Endoglin.

Possible Etiology Early Onset Preeclampsia

- The immune system also plays an important role in this process. Recent studies suggest that uterine natural killer cells at the maternal fetal interface produce factors which promote migration of the invasive trophoblast cells and death of the arterial endothelial cells. This suggests that a cross talk between trophoblasts and immune cells is important in early placentation and spiral artery remodelling (Fraser et al. J Pathol 2012)
- Uterine NK cells isolated from women at risk of PE failed to induce death of arterial endothelial cells and as such this might contribute to impairing spiral artery remodelling, thus contributing to the development of PE.

Possible Etiology Early Onset Preeclampsia (PE)

Clinically, this results in multisystem damage, including hypertension, renal and liver dysfunction and importantly, placental insufficiency and fetal growth restriction

Placental Pathology and Early Onset PE

- Specific placental pathological defects have been consistently noted in association with early onset PE
- These include infarcts, abruptio, villous maldevelopment and decidual vascular defects



Evidence of intraplacental bleed on ultrasound

Placental pathologies - Eclampsia

Who is at risk?

•Some women are at higher risk in getting pre-eclampsia and consequently developing eclampsia. Listed below are some of the women that are at higher risk of contracting this condition:

- Primigravidae
- Pregnant teens and women over 40
- History of chronic essential hypertension, diabetes or renal disease
- Obesity
- Multiple pregnancies
- Family history of pre-eclampsia
- Diabetes mellitus
- Previous history of pre-eclampsia
- Autoimmune disorders
- Vascular and cardiac diseases
- African American ethnicity

For several of these risk factors, the risk of PE can be as high as 25%



Identifying the woman at risk

- Based uniquely on maternal clinical and historical factors, the identification of the “at risk” woman will categorize more than 60% of pregnant women as high-risk and predicts less than 30% of those destined to develop PE, at a false-positive rate of 10% (Obstet Gynecol. 2010;115(6):1233-8)
- A “model” is likely more realistic as a clinical tool in the prediction of those at true risk of PE

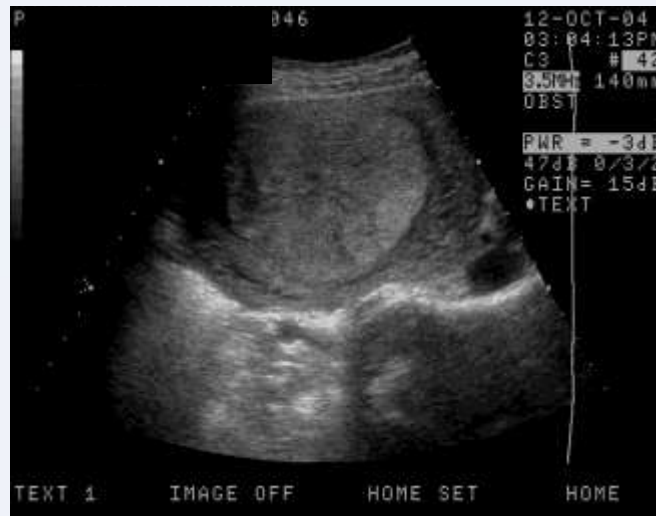
Identifying the woman at risk

Several tools are available to improve the adequate identification of at risk women

- Uterine Artery Doppler: increased resistance in the uterine artery detected by a first trimester ultrasound significantly improves the proper identification of the woman at risk
- Biomarkers: several biomarkers have been shown to be somewhat predictive of PE including PAPP-A, AFP, s-Flt, sEndoglin and PP-13 amongst others.

Identifying the woman at risk

- Placental sonogram: the presence of a small, heterogeneous or thick placenta on ultrasound is associated with an increased risk of PE



No single marker or clinical finding is an appropriate stand alone predictor of PE

Prevention

- Once the patient at risk has clearly been identified, a referral to the Placental Health Clinic can be initiated.
- Potential preventative approaches such as the use of aspirin will then be evaluated as appropriate.
- The current literature strongly suggests an increased risk of later cardiovascular disease in the woman who suffered early onset PE. As such, appropriate follow-up is recommended.

Placental pathologies – Fetal growth restriction (FGR)

What is FGR and what are the causes?

- Fetal growth restriction is defined as the inability for the fetus to attain its growth potential. In general it is diagnosed when the estimated fetal weight on ultrasound is below the 5th centile although some prefer to use the 3rd percentile.
- It must be distinguished from “small for gestational age” which is defined as a fetus whose estimated weight falls below the 10th centile. Many of those infants are merely constitutionally small and are otherwise completely healthy.
- There are multiple causes of fetal growth restriction including genetic, nutritional, infectious and environmental. The majority is however due to uteroplacental insufficiency

Relevance of FGR

FGR is associated with significantly increased risks of:

IUFD

fetal distress

cesarian section

Perinatal mortality

Sepsis

Metabolic abnormalities

Etc..

Relevance of FGR

Literature also supports increased risks of adult onset diseases such as:

Diabetes

Obesity

Metabolic syndrome

Hyperlipidemias

Hypertension

Cardiovascular disease

Psychiatric pathology

Role of ultrasound

- Sonography is the diagnostic tool for FGR
- A complete intrauterine (fetal and placental) and vascular evaluation is very important.
- This includes the possible identification of markers of aneuploidy or infection and also will provide clues as to the possibility of uteroplacental insufficiency being the culprit

Role of ultrasound

Uteroplacental insufficiency will be strongly suspected in the presence of:

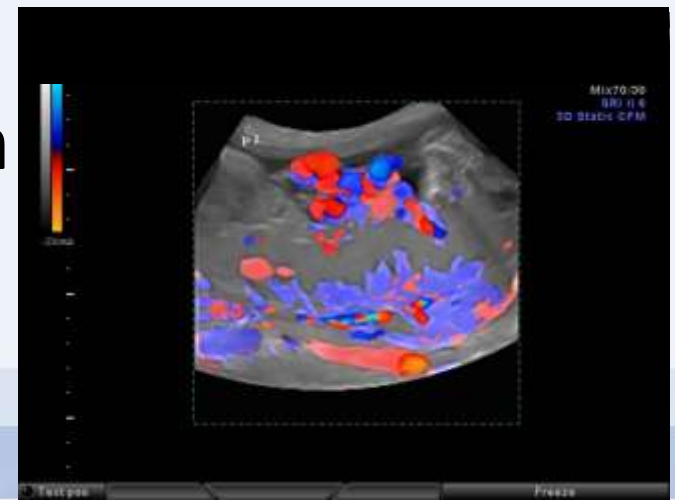
Oligohydramnios

A short, heterogeneous or globular placenta

Increased resistance in the umbilical artery

Changes in the middle cerebral artery or in the fetal venous system

Poor placental vascular pattern



Early identification-First trimester: Crown Rump Length

- 4229 pregnancies
- first-trimester crown-rump length (CRL) 2-6 days smaller than expected, on the basis of an accurate menstrual history, was associated with an increased risk of a birth weight below 2500 g at term (relative risk (RR) 1.8, 95% CI 1.4-3.8) and a birth weight below the 5th centile (RR 3.0, 95% CI 2.0-4.4)

Smith et al NEJM 1998

Early identification-First trimester: Crown Rump Length

- Prospective cohort study of 976 women who conceived as the result of assisted reproductive technology
- One hundred and thirteen (11.5%) small for gestational age infants (<10th centile) were born
- The risk of delivering a small for gestational age infant varied inversely with first trimester growth (ROC 0.73)

BMJ. 2007 Apr 21;334(7598):836.

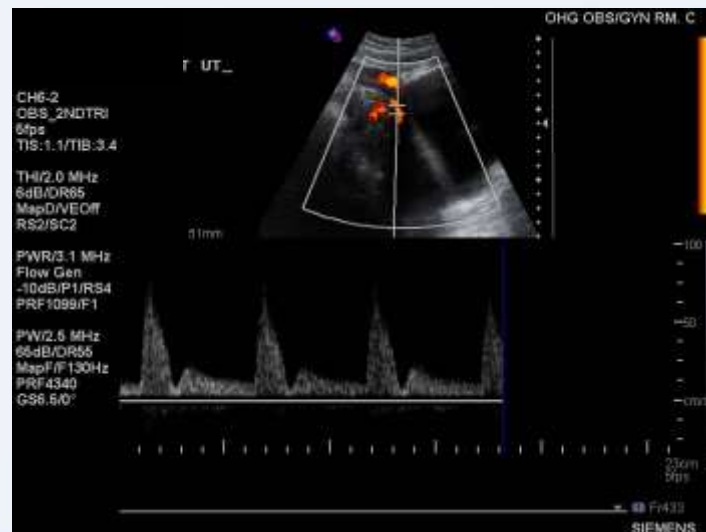
Early identification-First trimester: Crown Rump Length

- First-trimester CRL was positively associated with second- and third-trimester head circumference, femur length, and estimated fetal weight
- First trimester CRL was associated with postnatal weight until the age of 11 months!

JAMA, February 10, 2010—Vol 303, No. 6

Early identification-Doppler

- FASTER trial: 1067 women
- Mean RI at or above the 75th percentile (0.70) was associated with a 5.9 times greater risk of IUGR (AJOG 2005 Sep;193(3 Pt 2):1208-12)



Early identification-Doppler

- Meta analysis: 61 studies of intrauterine growth restriction (total 41 131 patients)
- Major Findings:
 - UA Doppler more sensitive in T2 vs T1
 - UA Doppler more predictive of PET vs IUGR

CMAJ. 2008 March 11; 178(6): 701–711

Placental Sonogram

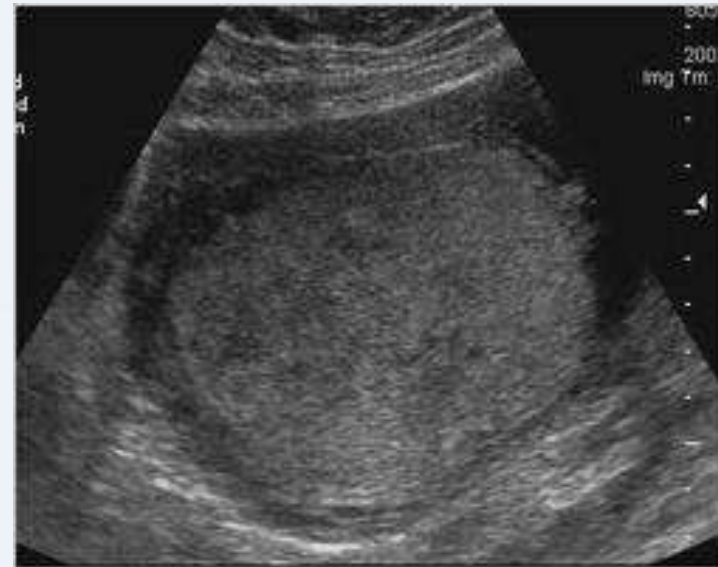
- Size
- Thickness
- Echogenicity
- Heterogeneity
- Globular placenta

Placental Sonogram

- Using panoramic view, length < 11 cm at 18-20 weeks correlates with risk of LBW (Pearson: 0,317, $p=0,026$, sensitivity 60%, specificity 90%) (Gruslin et al, Placental Health Clinic)

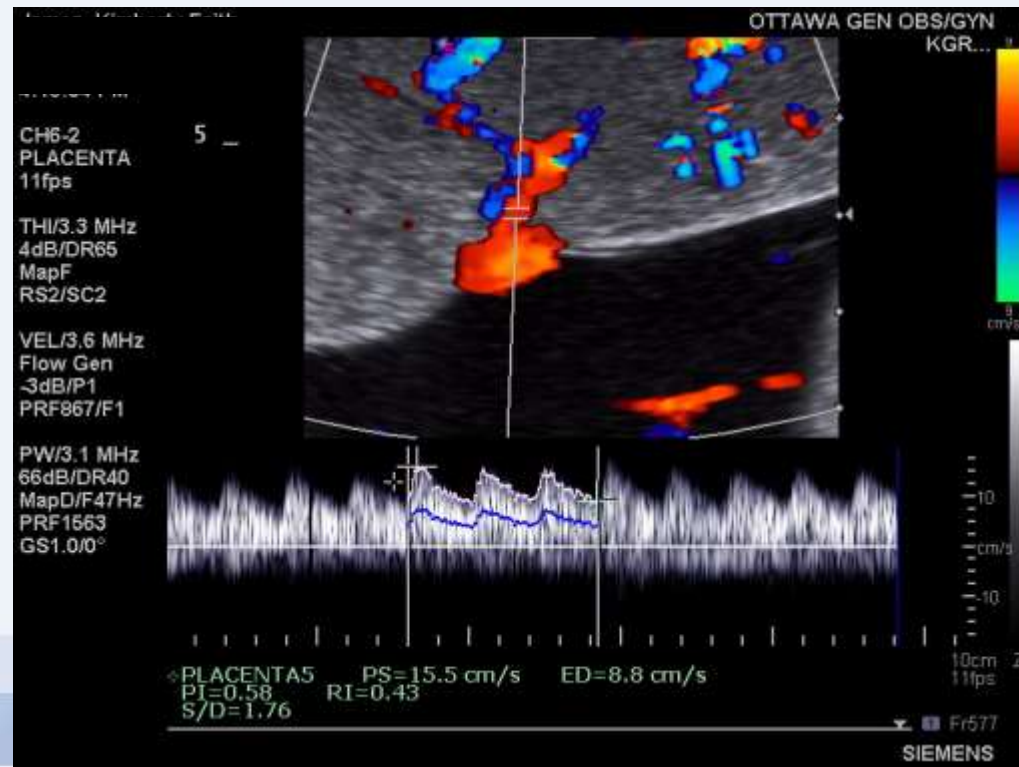


Thickness/echogenicity/heterogeneity/shape



Placental Doppler

An increased resistance (PI) in the intravillous vessels was associated with risk of PET and/or FGR as early as 18-20 weeks gestation ($p=0.0003$) (Gruslin et al. Placental Health Clinic)

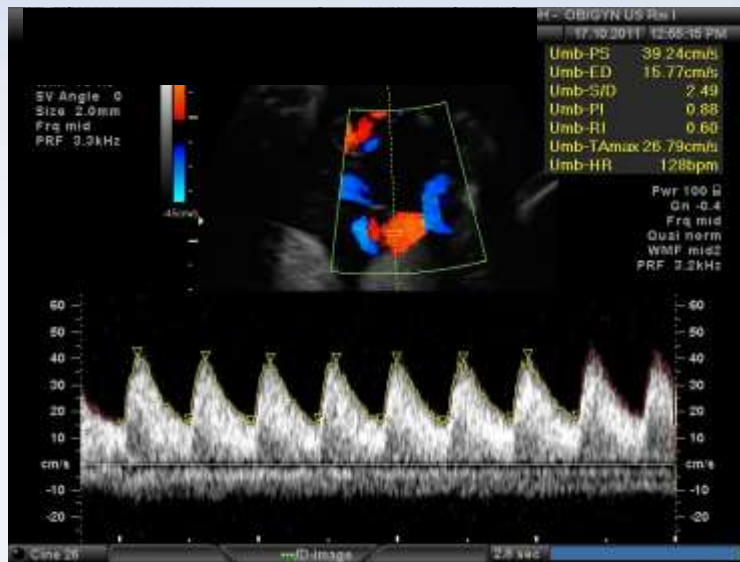


Evaluation of the FGR

Umbilical artery Doppler

- Distinguishes between FGR and SGA
- In FGR, decrease number of villi and stem vessels lead to increased resistance: AEDF, REDF (risk distress):interval to delivery 1-26 days
- Decreases perinatal morbidity and mortality in FGR (30%)
- BEST clinical method to assess fetal compartment of the placental circulation

Umbilical Artery Doppler



Normal UA flow



Reversed end diastolic flow

Middle cerebral artery Doppler

Chronic hypoxia (early onset FGR)



baroreceptors/chemoreceptors



cerebral artery vasodilatation

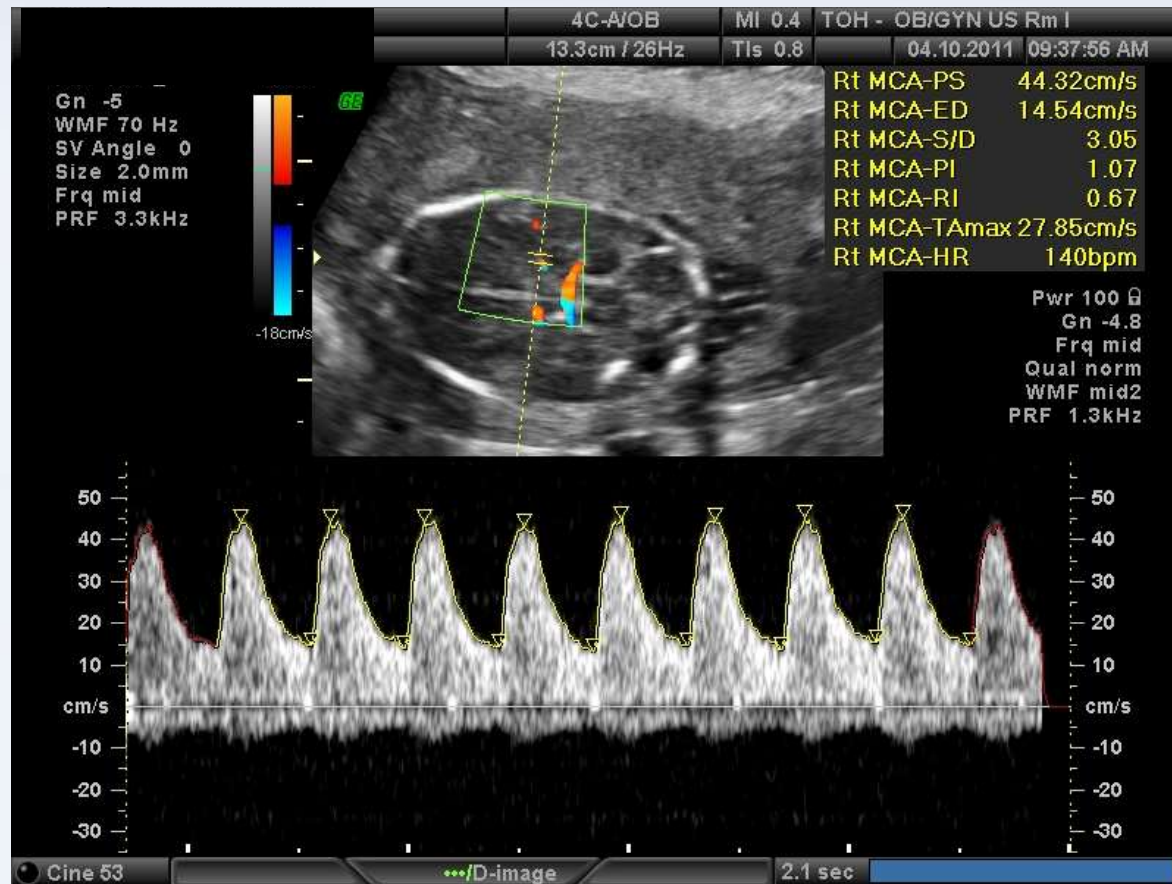


Increase in diastolic blood flow velocity



decrease MCA PI or decrease MCA PSV prior to deterioration or demise

Middle cerebral Artery Doppler



Redistribution noted in early onset FGR

Middle cerebral artery Doppler: significance of redistribution

- Adaptation/protection?
- Hypoxemia?
- Early studies on neurodevelopmental outcome suggested that foetal brain sparing in IUGR was a benign adaptive process preventing severe

brain damage (Early Hum Dev 1998; 52(1): 67–79)

- More recently, it has been reported that term SGA fetuses with isolated MCA redistribution may be at risk of abnormal neonatal neurobehaviour and suboptimal neurodevelopment at 2 years (Ultrasound Obstet Gynecol 2009)

Middle cerebral artery Doppler: significance of redistribution

- *Cohort 89 VLBW fetuses followed with antenatal Doppler:*
 - an abnormal UA-PI/MCA-PI ratio was associated with lower cerebral volume (mean 330 (SD 40.4) mL) than those infants with a normal UA-PI/MCA-PI ratio (mean 371 (SD 50.2) mL)
 - High UA-PI/MCA-PI ratio was associated with an increased incidence of brain pathology and abnormal cognitive performance

Ultrasound Obstet Gynecol 2010; **36**: 178–185.

Middle cerebral artery Doppler: significance of redistribution

Very careful interpretation

May be helpful in specific groups-likely more significant in late FGR (>34 weeks)

- cerebral artery Doppler studies in early onset FGR provide little additional information over those utilizing UA Doppler alone
- In late FGR, cerebral artery Doppler studies provide important new findings as regional alterations in blood flow resistance and the pattern of observed developmental abnormalities suggest an increased vulnerability of frontal lobe areas

Baschaat *Ultrasound Obstet Gynecol* 2011; **37**: 501–514

Abnormal ductus venosus Doppler

Abnormal DV in FGR associated with:

- acidaemia
- increased perinatal mortality (60-100%)
- considered a marker of acid base status
- occurs with advanced severe disease
- precedes abnormal BPP by 48-72 hrs

Fetal Surveillance

NIH Recommendations (*Obstet Gynecol.* 2009):

- Abnormalities in Doppler velocimetry indices may help distinguish between fetal growth restriction due to placental insufficiency, in which impedance indices tend to be increased, and growth restriction from other causes
- There are no data from randomized trials indicating the optimal mode and frequency of antenatal testing of the fetus with growth restriction

Fetal Surveillance

Cochrane review: **Regimens of fetal surveillance for impaired fetal growth (2009):**

“There is almost no evidence to date to indicate an optimal antenatal surveillance method for infants identified with impaired growth.”

Fetal Surveillance

- BPP:
 - Not reliable in the preterm IUGR because of false positives and false negatives (Am J Obstet Gynecol 2008)
- evidence from randomised trials does not support the use of BPP as a test of fetal wellbeing in high-risk pregnancies (Cochrane review 2009)

Fetal Surveillance

- Likely requires integrated testing including:
 - First trimester
 - Evaluation of growth profile and velocity in the context of GA
 - Evaluation of amniotic fluid volume
 - Evaluation of fetal activity (BPP?) and CTG
 - Evaluation of Doppler indices- Doppler studies of the umbilical artery *should be incorporated* in the protocols for fetal monitoring in high-risk pregnancies thought to be at risk of placental insufficiency (Cochrane review 2010)

Conclusion

- FGR may be a difficult diagnosis (overlap)
- Most is secondary to placental insufficiency
- Assess biometry in T1 (CRL) and T2 (Abdominal circumference)
- Assess amniotic fluid volume
- **Placental sonogram**
- Evaluate evidence of uteroplacental insufficiency
- Essential to send placenta for pathological evaluation
- At risk women can be seen for evaluation, consult and/or F/U in the Placental Health Clinic

Interesting facts about pregnancy

Traditions

- While most North Americans throw out the placenta after birth, other countries have different traditions regarding this organ. Different cultures will have different rituals to honour newborns along with the placenta which has a big impact during pregnancy.

- Indonesia – On the day of birth, the father will clean, wrap and bury the placenta which will act as the babies guardian angel. The placenta is perceived as the baby's twin which is why it must be buried according to their tradition.

- China – In this country, the placenta is seen as a force of life. They will dry it and then add it to recipes in order to consume it to increase vitality and energy.

- Africa – In certain regions of this country, the placenta is wrapped up in blankets and planted under a tree. The tree then symbolizes ongoing life.

- Europe – In certain tribes, the placenta is said to have its own spirit and is washed and then buried by the father in a shady place. If it is not done properly, it is believed that the mother or baby will become very sick.

- South America – In some regions, the placenta is burnt and planted in the ground in order to protect them from evil spirits.

