بسم الله الرحمن الرحيم

Pregnancy & Lactation 1

FINAL | Lecture 6

﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾

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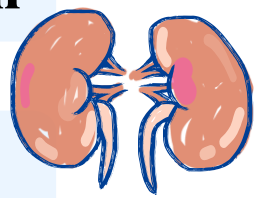
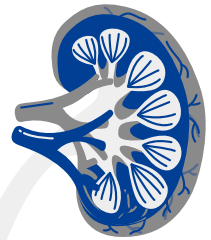
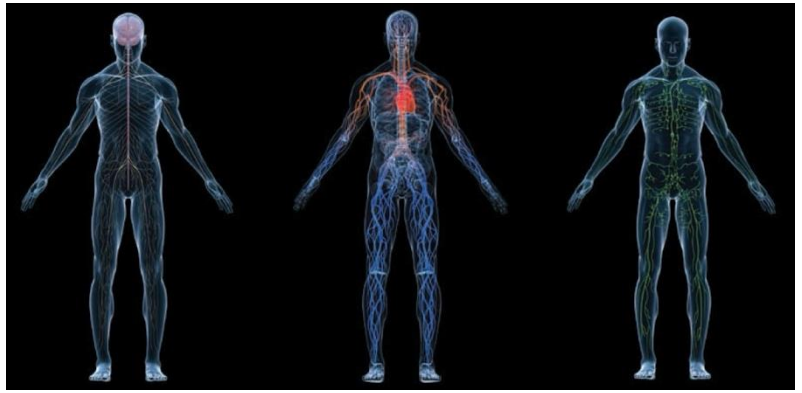




اللهم احفظ لنا أمهاتنا، وارزقنا برّهن ورضاهن، وبارك لنا في أعمارهن وصحتهن، واجعل السعادة والطمأنينة تلازمهن في كل حين.
اللهم وارحم الأمهات المتوفيات، واغفر لهن، ونوّر قبورهن، واجعلها روضة من رياض الجنة، وأكرم نزلهن يا أرحم الراحمين.



PREGNANCY AND LACTATION

EBAA M ALZAYADNEH

CHAPTER 83 GUYTON

PHYSIOLOGY DEPARTMENT

Lecture I

OBJECTIVES

By the end of the 2 lectures, you should be able to:

- Describe fertilization
- Recognize the development and the function of the placenta
- Recognize the placenta as an endocrine organ
- Describe the physiological functions of placental hormones
- Explain the mother's physiological response to pregnancy
- Describe labor and its stimulation
- Understand hormonal mechanisms of lactation

Initiation of Fertilization

- The 1st stage of Fertilization and pregnancy is when the sperm penetrates the granulosa cells surrounding the oocyte -corona radiata cells- and then the zona pellucida by proteolytic enzymes released from spermal acrosome.
- After penetration, the oocyte resumes meiosis II forming the mature ovum (which carries 23 chromosomes in its pronucleus) plus a second polar body that is expelled.
- On entering the ovum, the sperm‘s head swells to form a male pronucleus (contains 23 chromosomes).
- This process takes place in the ampulla of uterine tube.
- Later, the 23 unpaired chromosomes of the male pronucleus and the 23 unpaired chromosomes of the female pronucleus align themselves to re-form a complete complement of 46 chromosomes (23 pairs) in the fertilized ovum or zygote.

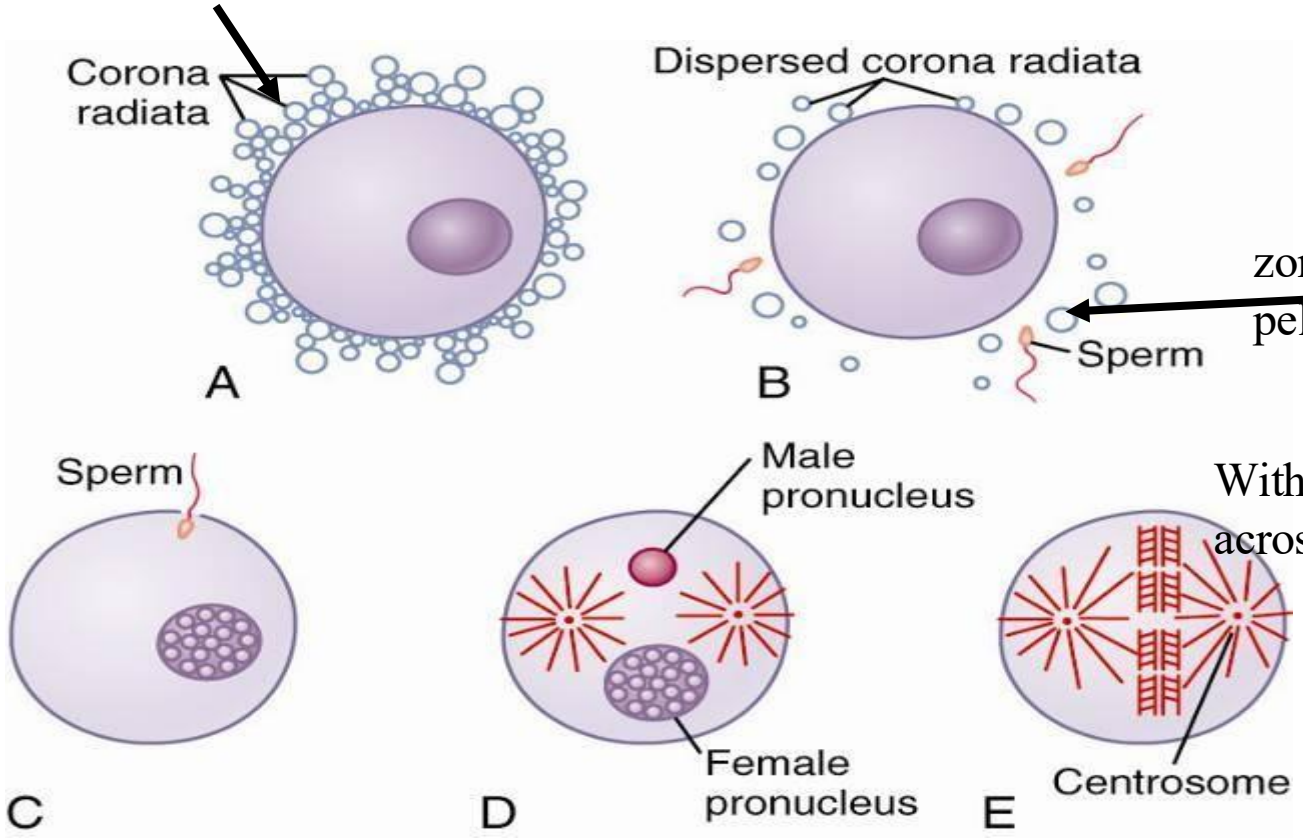
Continued…

- At this stage, the zygote is ready to undergo several divisions initiating actual fetal development.

- What's interesting about fertilization is that Only **ONE** sperm (out of few thousand sperms reaching the ampulla) can penetrate the zona pellucida and eventually the oocyte; because once one sperm reaches and fuses with the oocyte plasma membrane, the oocyte becomes activated and the intracellular calcium inside the oocyte increases.
- The Ca^{2+} surge causes cortical granules beneath the oocyte membrane to exocytose their contents into the space between the membrane and zona pellucida. Those contents include enzymes that modify zona pellucida receptors making them harder and impermeable to other sperms.

- Sperm penetrates *corona radiata* and *zona pellucida* (hyaluronidase)
- Oocyte divides to form **mature ovum**
  - (female pronucleus 23 unpaired chr)
- Head of sperm swells
  - (male pronucleus 23 unpaired chr)
- release of cortical granules preventing
  - further sperm penetration
  - Both pairs Align
- Fertilized ovum (zygote) contains 23 paired

Granulosa cells



Fertilization:
End second meiosis in ovum

Fertilization of the ovum. **A**, The mature ovum sur rounded by the corona radiata. **B**, Dispersal of the corona radiata **C**, Entry of the sperm. **D**, Formation of the male and female pronuclei. **E**, Reorganization of a full complement of chromosomes and beginning division of the ovum.

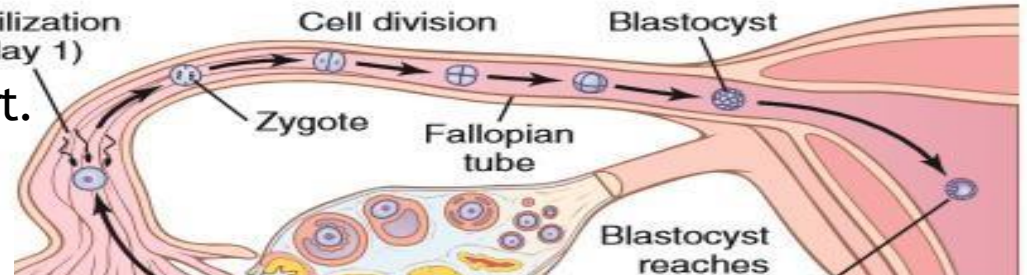
GENDER OF THE BABY

- Y chromosome VS X Chromosome of (sperm or Ova?)

  What determines the gender of the fetus created is the **sex chromosome of the fertilizig sperm.**

After ejaculation, sperms reach ***ampulla*** of fallopian tube within 30-60 min (by PG (prostaglandins from male seminal fluid) and OT (oxytocin from posterior pituitary) actions)

Ampulla of oviduct-opt. site of fert.



Location	Time of appearance (min after ejaculation)	Percent of ejaculated sperm*
Fertilization site (upper third of oviduct)	30–60	0.001
Uterus	10–20	0.1
Cervical canal	1–3	3

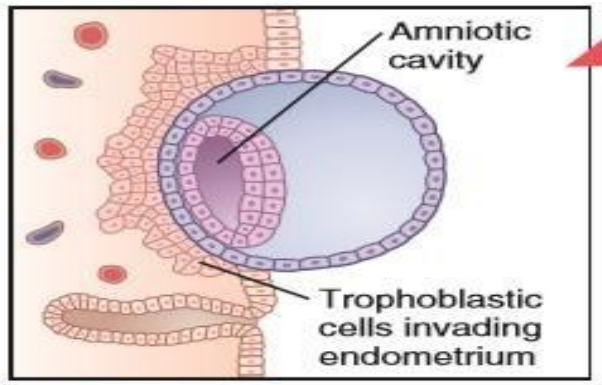


Figure 83-2. A, Ovulation, fertilization of the ovum in the fallopian

Figure Ovulation, fertilization of the ovum in the fallopian tube, development of the blastocyst, and implantation in the endometrium.

For a good fertility, there is a need for high number of sperms; because only 0.001% of ejaculated sperms succeed reaching the site of fertilization after 30-60 minutes of ejaculation.

Ova can enter the other side

Transport of fertilized ovum

- After the first cell division (mitosis), the zygote starts moving toward the isthmus of the uterine tube, where spastic contractions of the tube impede further movement towards the uterus until reaching the blastocyst stage after about 3 days, where the zygote have undergone multiple divisions.
- After this stage, the rapidly increasing progesterone secreted by the ovarian corpus luteum first promotes increasing progesterone receptors on the fallopian tube smooth muscle cells; then the progesterone activates the receptors, relaxing the tubules and allowing entry of the ovum into the uterus.
- As a result of the mentioned delay, (in addition to the rugged cryptoid surface of fallopian tube that impedes passage of the ovum despite the fluid current) the ovum needs 3-5 days after fertilization to reach the cavity of the uterus, where implantation occurs.

TRANSPORT OF FERTILIZED OVUM

- 3-5 days after fertilization, the zygote reaches uterine cavity
- **Transport:** fluid current + action of cilia + weak contractions of the fallopian tube exerted by oxytocin, this can enhance the transport of the zygote
- Isthmus (last 2cm) contracts (first 3 days) then relaxes under effect of progesterone which allows the zygote to enter the uterus
- Delayed transport allows proper cell division
- Blastocyst (100 cells) enters the uterus
- Nutrition inside the uterus cavity before implantation is by uterine milk

While in the uterine tube, the ovum receives nutrients from the tubal secretions and at either stages ,all these fluids are secreted under progesterone effect

IMPLANTATION

- Implantation results from the action of trophoblast cells that develop over the surface of the blastocyst. These cells secrete proteolytic enzymes that digest and invade the adjacent cells of the uterine endometrium .

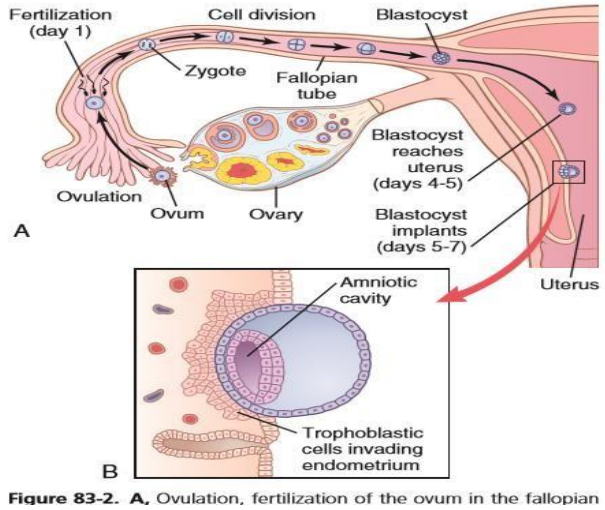


Figure 83-2. A, Ovulation, fertilization of the ovum in the fallopian

- Blastocyst remain in uterine cavity 1-3 days b4 implant (conceptus)
- It occurs 5th to 7th day of ovul
- Decidua : endomet cells swell under progest (nutrients) up to 8 weeks
- Trophoblastic cells-cords (proliferation) from blastocyst
- Blood capillaries grow in the cords
- 21 days after fertilization, blood starts to be pumped by fetal heart into the capillaries
- Maternal blood sinuses develop around the trophoblastic cords because of the exchange between the maternal and fetal blood
- More and more trophoblast projections develop (placental villi)
- Placenta supply: begins 16th day

Nutrition of the ovum

- **Before implantation**, the developing embryo is nourished by secretions from the female reproductive tract. While in the uterine tube, it receives nutrients from tubal secretions, whereas after reaching the uterine cavity and before implantation, it is supported by nutrient-rich endometrial secretions known as uterine milk. All those secretions are produced mainly under the influence of **progesterone**.

- **After implantation**, decidua is the main source of nutrients.

  Decidual cells are endometrial stromal cells containing extra quantities of glycogen, proteins, lipids, and even some minerals necessary for development of the conceptus, they are secreted under the influence of progesterone. The trophoblasts will digest these cells to get the nutrition from them because there is no placenta yet.

- The embryo contiues to obtain at least some of its nutrition in this way for up to 8 weeks, although the placenta also begins to provide nutrition after about the 16th day beyond fertilization (a little more than 1 week after implantation).

Examine these figures carefully before moving up to the next slide

Organization of the mature placenta and intervillus space.

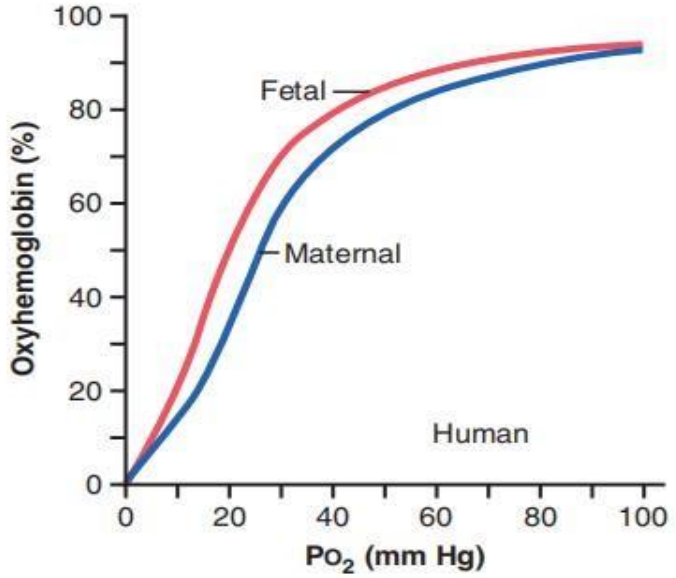


Figure 83-6. Oxygen-hemoglobin dissociation curves for maternal and fetal blood, showing that fetal blood can carry a greater quantity of oxygen than can maternal blood for a given blood Po_2. *(Data from Metcalfe J, Moll W, Bartels H: Gas exchange across the placenta. Fed Proc 23:775, 1964.)*

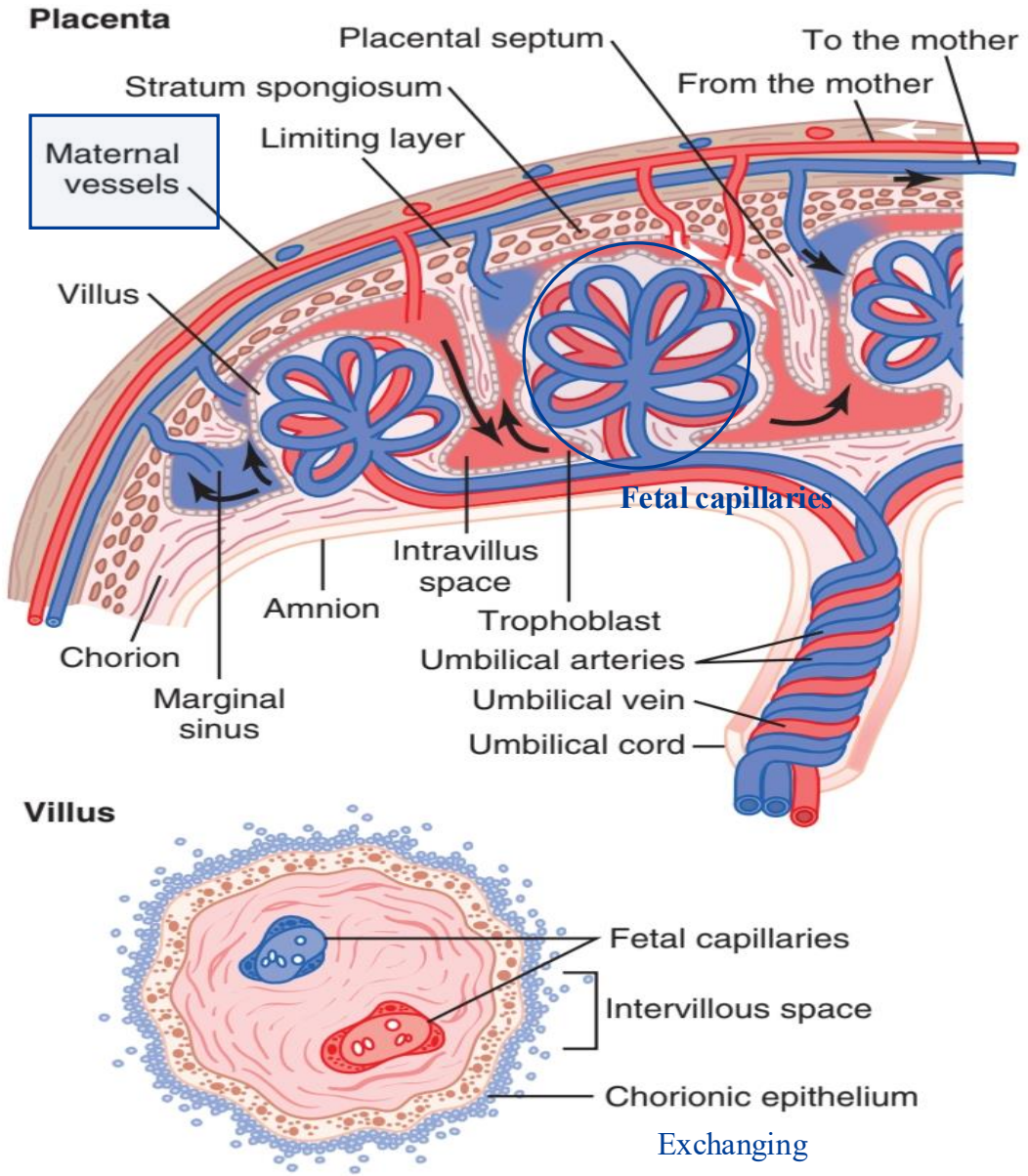


Figure 83.5 *Top*, Organization of the mature placenta. *Bottom*, Relationship of the fetal blood in the villus capillaries to the mother's blood in the intervillous spaces.

Placental development

- Once implantation has taken place, the trophoblast cells and other adjacent cells from the blastocyst and the uterine endometrium proliferate rapidly, forming the placenta and the fetal membranes.
- The trophoblast develops into finger-like projections called **chorionic villi** (previously trophoblastic villi), which are the main sites of maternal-fetal exchange.
- Blood sinuses supplied with blood from the motherës uterine arteries start developing around the outsides of the trophoblastic cords.
- Thus, the villi, carrying fetal blood, are surrounded by sinuses that contain maternal blood.

Placental function

- The fetus is connected to the placenta by the umbilical cord which consists of 2 arteries and 1 vein.
- Umbilical vein delivers oxygenated blood from the placenta to the fetus, and the 2 umbilical arteries deliver the deoxygenated blood from the fetus to the placenta.
- Trophoblastic villi are the medium where blood and nutrient exchange occur.
- Maternal blood from the uterine artery diffuses through the trophoblastic cells supplying fetal umbilical vein with nutrients and oxygenated blood while carbon dioxide and metabolic waste products diffuse from the fetal umblilical arteries into the maternal uterine vein.

- In other words:
  - Maternal blood (oxygenated) is delivered to the placenta by the uterine arteries. After giving oxygen and nutrients, it returns deoxygenated via uterine veins.
  - Fetal blood (deoxygenated) leaves the fetus through the 2 umbilical arteries → to the placenta.
  - Oxygenated blood then returns to the fetus via the umbilical vein.

Pregnancy hormones

- hCG – secreted by blastocyst (6-8 cells) then syncytiotrophoblasts: It is secreted **early** by the **blastocyst**, then later by the **trophoblast**, which differentiates into two layers: the **syncytiotrophoblast and the cytotrophoblast**. The **syncytiotrophoblast secretes hormones, including steroids and hCG.**

- Detected within 8-9 days of conception (maternal blood and urine)

- maintains Corp.L and Decidua: **hCG hormone** is important for prolonging the life of the **corpus luteum** which increases progesterone secretion. Progesterone helps maintain pregnancy, makes the decidua more swollen, and promotes the production of nutrients important for the implanted conceptus. It also decreases uterine contractions to prevent expulsion of the conceptus.

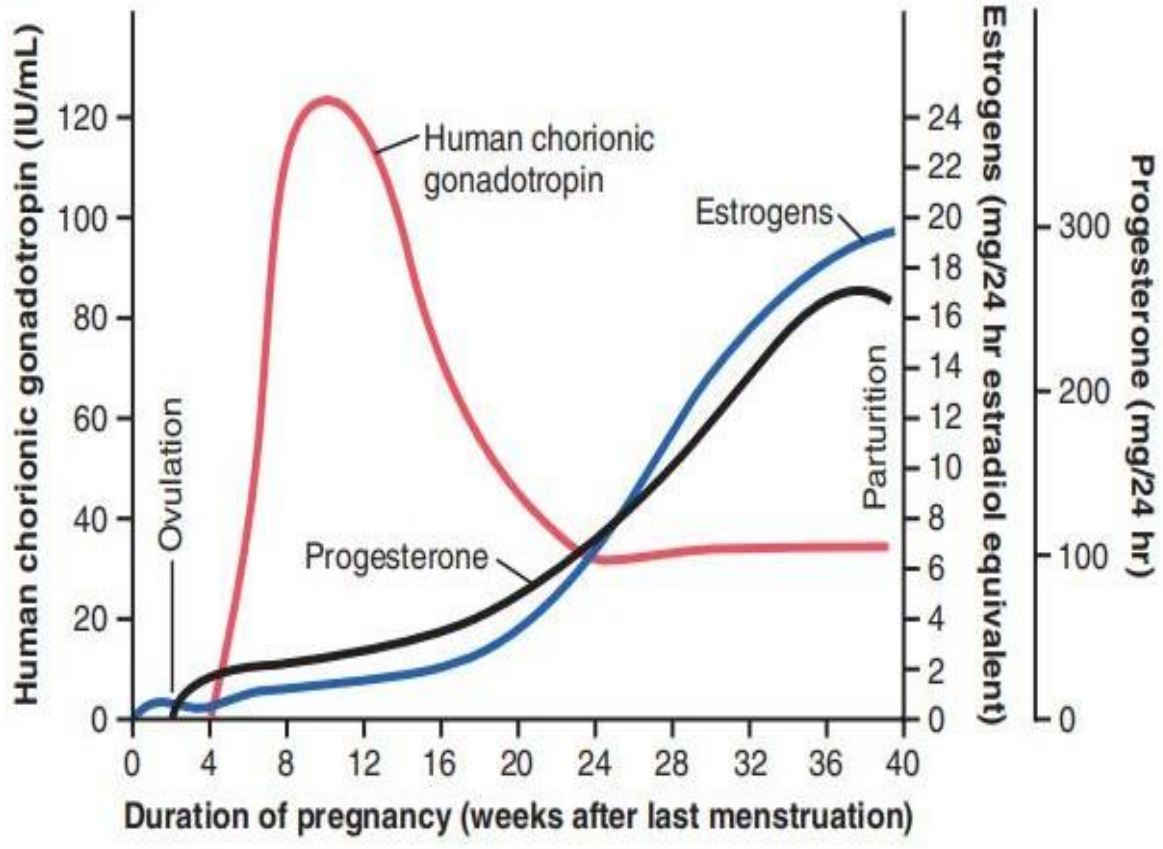
- If CL removal, week 6^{th}-12^{th} abortion.

- 13^{th} CL involute so hCG is most important during the first trimester of pregnancy, although it continues to have other functions throughout the rest of pregnancy, such as stimulating testosterone secretion by fetal Leydig cells in the second trimester (Lecture 5).

Pregnancy hormones

- This figure shows that **hCG** begins to increase markedly **around week 4** after the blastocyst stage and reaches its maximum level **around week 10**. After that, it starts to **decline until weeks 16–20**, then remains at a **relatively stable level for the rest of pregnancy (doesn't reach zero).**

- At first, **progesterone levels increase more than estrogen levels** during the **first** and **middle** trimesters. However, during the **last** trimester, **estrogen levels become higher.**



Functions of hCG

1. Produced by syncytiotrophoblasts (8-9 d after fertilization)
2. Maintains corpus luteum beyond normal (day 26 of the cycle) lifespan
3. Stimulates progesterone and E2 (estradiol) by CL (corpus luteum)
4. Stimulates essential DHEA-S (androgen) in fetal zone of adrenal gland
5. Stimulates testosterone production in male fetus –male organs and descending testes. Testosterone levels increase during early pregnancy and are essential for the development of male organs. Without testosterone, the fetus will remain with female organs. The main stimulus for the interstitial cells to become Leydig cells and secrete testosterone is hCG during early pregnancy, as hCG acts similarly to LH.
6. hCG receptors in endometrium and myometrium and can inhibit contractions produced by oxytocin through increasing progesterone secretion.
7. Immunosuppressant to help prevent rejection of the conceptus.

Trophoblasts differentiation

During division and early development, trophoblasts differentiate into 2 layers:

- inner - cytotrophoblast -- well-defined cells, rapidly proliferating—invade spiral arteries

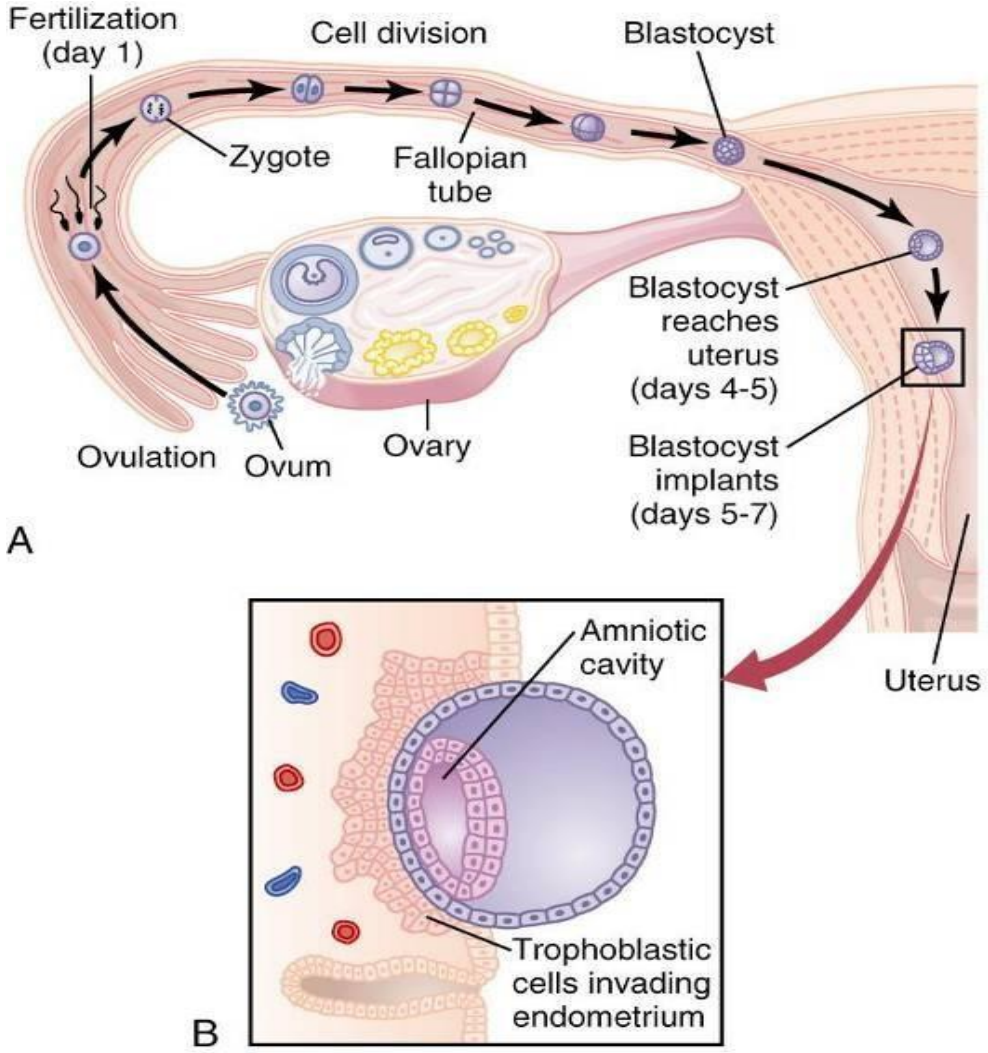
- outer - syncytiotrophoblast -- multinucleated mass without cellular boundaries -- placental steroid and hormone and hCG production -- line intervillus space, opposite of deciduum -- exposed directly to maternal blood

Protrusions release TNFα -- penetrates basement membrane of uterine epithelial cells and to help cells reach the uterine stroma

Implantation

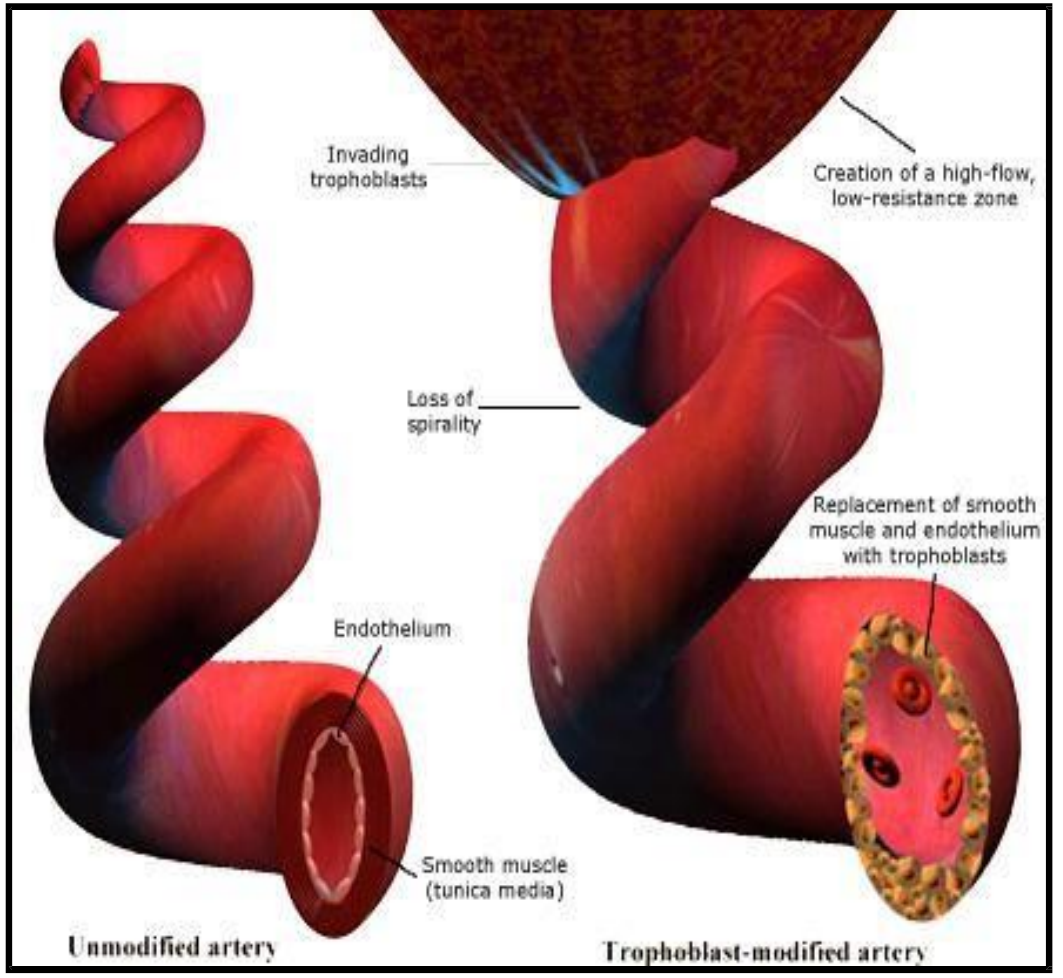
- Implantation of the blastocyst, invasion of cyto- and syncitio-tropho-blasts.

Implantation occurs around **days 5–7.** After invasion of the cytotrophoblast and syncytiotrophoblast, the **amniotic cavity, fluid, and membranes** begin to develop, in addition to the **cells that will form the fetus.**



Spiral Arteries

This image demonstrates the process of invasion by the **cytotrophoblasts into the spiral arteries**. Notice the difference between the normal (unmodified) artery on the left and the artery on the right, where the **endothelium and smooth muscle have been completely replaced by cytotrophoblast cells.**



Pregnancy hormones

Factors which contribute to trophoblast differentiation: growth factors (IGF, TGF, EGF) and cytokines
Cytotrophoblasts and syncytiotrophoblasts /placental- hypothalamic-pitutiary relation:

Early pregnancy:

- Placenta (syncytiotrophoblast) → **hCG**
- hCG acts like **LH**
- Maintains corpus luteum → progesterone as well as estrogen continues

Later pregnancy:

- Placenta produces:
  - **Estrogen**
  - **Progesterone**

These hormones **suppress GnRH, LH, FSH** **(negative feedback)** that's why follicular development is suppressed during pregnancy.
So: Normal axis (Hypothalamus → Pituitary → Ovary) is **suppressed**

Placenta becomes the **dominant endocrine controller**

Nutrition of the fetus

- This figure shows the source of nutrients during pregnancy from week 4 to weeks 11–12. During the **early weeks,** the main source of nutrition is through **the trophoblast,** which digests the stored materials in the decidua to obtain nourishment. Later, this overlaps with **placental development around week 10**, when the **placenta gradually begins supplying nutrients from the mother to the baby.**

- At the beginning, the level of nutrition is **low because the baby's nutritional needs are also low**. Nutrient supply then gradually **increases until the end of pregnancy.** From around **week 12 until the rest of pregnancy, the placenta becomes the main source of nutrition.**

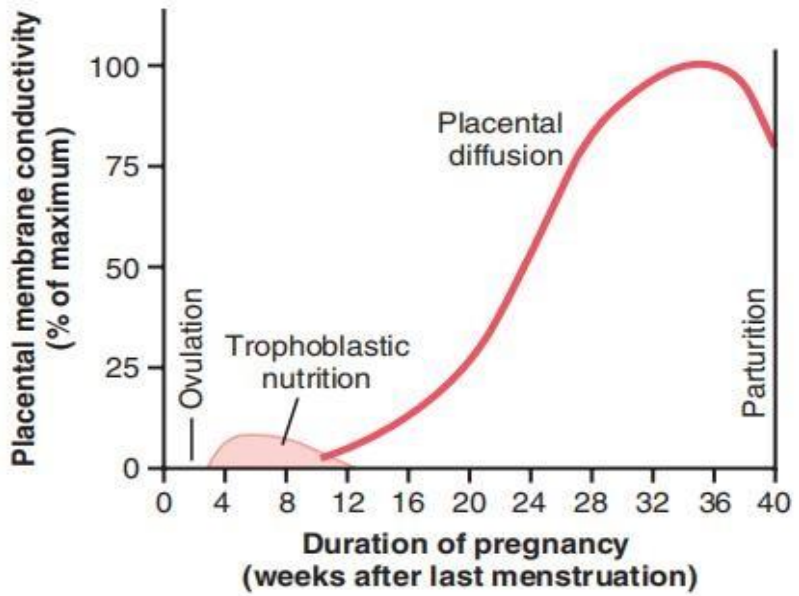


Figure 83-4. Nutrition of the fetus. Most of the early nutrition is due to trophoblastic digestion and absorption of nutrients from the endometrial decidua, and essentially all the later nutrition results from diffusion through the placental membrane.

Functions of the placenta

1. Fetal gut in supplying nutrients
2. Fetal lung in exchanging O2 and CO2 as fetal lungs are considered **functionally inefficient.**
3. The fetal kidney in regulating fluid volumes and disposing of waste metabolites
4. Endocrine gland synthesizing many steroids and protein hormones that affect both maternal and fetal metabolism

DIFFUSION IN PLACENTA

- In the early months of pregnancy, the placental membrane is still thick because it is not fully developed. Therefore, its permeability is low. Further, the surface area is small because the placenta has not grown significantly.Therefore, the total diffusion conductance is minuscule
- In later pregnancy, the permeability increases because of thinning of the membrane diffusion layers and because the surface area expands many times over, thus giving the tremendous increase in placental diffusion shown
- The mean pressure gradient for diffusion of oxygen through the placental membrane is about 20 mm Hg (50 mat-30 fet).
- The oxygen gradient is **about 20 mmHg,** which is adequate to supply the fetus, despite its **high growth rate and metabolic demands.** Although the placental surface area is **much smaller than the alveolar surface area,** this gradient is still able to provide sufficient oxygen to the fetus. SEE THE NEXT SLIDE

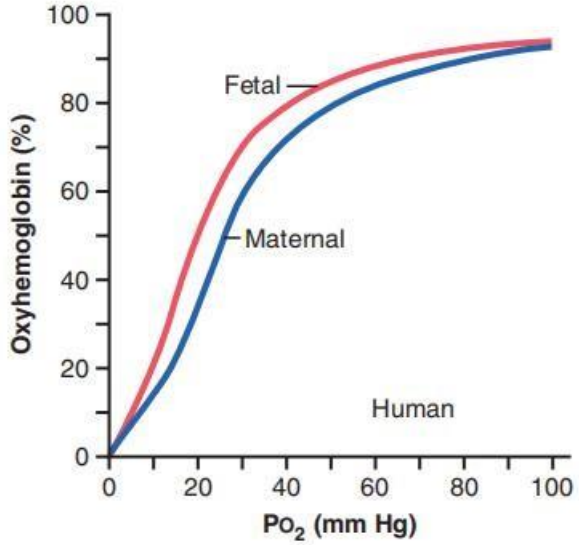
LOW O2 GRAD. BUT ENOUGH EXCHANGE

- First, fetal hemoglobin, curve of fetal hemoglobin is shifted to the left of that for maternal hemoglobin. (This means that at the low PO2 levels in fetal blood, the fetal hemoglobin can carry 20 to 50 percent more oxygen (higher affinity) than can maternal hemoglobin.)
- Second, the hemoglobin concentration of fetal blood is about 50 percent greater than that of the mother, more important factor in enhancing the amount of oxygen transported to the fetal tissues.
- Third, the **Bohr effect**, enhances the transport of oxygen by fetal blood. (hemoglobin can carry more oxygen at a low PCO2 than it can at a high CO2.) Loss of the carbon dioxide from baby to maternal makes the fetal blood more alkaline (more affinity for oxygen), whereas the increased carbon dioxide in the maternal blood makes it more acidic (promotes oxygen unloading)

OXYGEN EXCHANGE

- Total diffusing capacity of the entire placenta for oxygen at term is about 1.2 milliliters of oxygen per minute /mmHg gradient = 1.2*20 millilitres per minute

This figure shows the **oxygen saturation curves**: the **maternal curve** is on **the right,** while the **fetal curve** is shifted more to **the left**, indicating that fetal hemoglobin has a **higher affinity for oxygen.**



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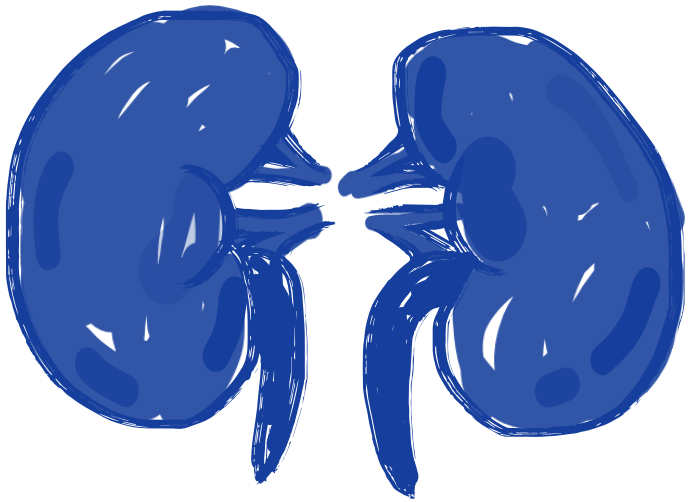
CO2 TRANSPORT

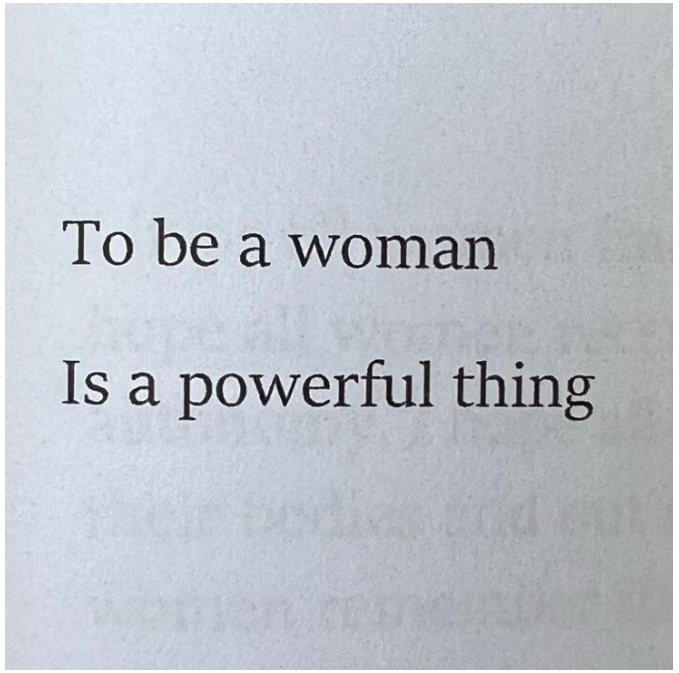
- The only means for excreting the fetal CO2 is through the placenta into the mother's blood.
- The partial pressure of carbon dioxide (PCO2) of the fetal blood is 2 to 3 mm Hg higher than that of the maternal blood (low gradient due to high solubility).
- Small but more than sufficient to allow adequate diffusion of carbon dioxide
- Due to the extreme solubility of carbon dioxide in the placental membrane allows carbon dioxide to diffuse about **20** times as rapidly as oxygen.



PHYSIOLOGY QUIZ LECTURE 6

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	18	so hCG is important until week 12	hCG is most important during the first trimester of pregnancy, although it continues to have other functions throughout the rest of pregnancy, such as stimulating testosterone secretion by fetal Leydig cells in the second trimester (Lecture 5).
V1 → V2			