PHYSIO

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Important

Pregnancy and Lactation

Chapter 83

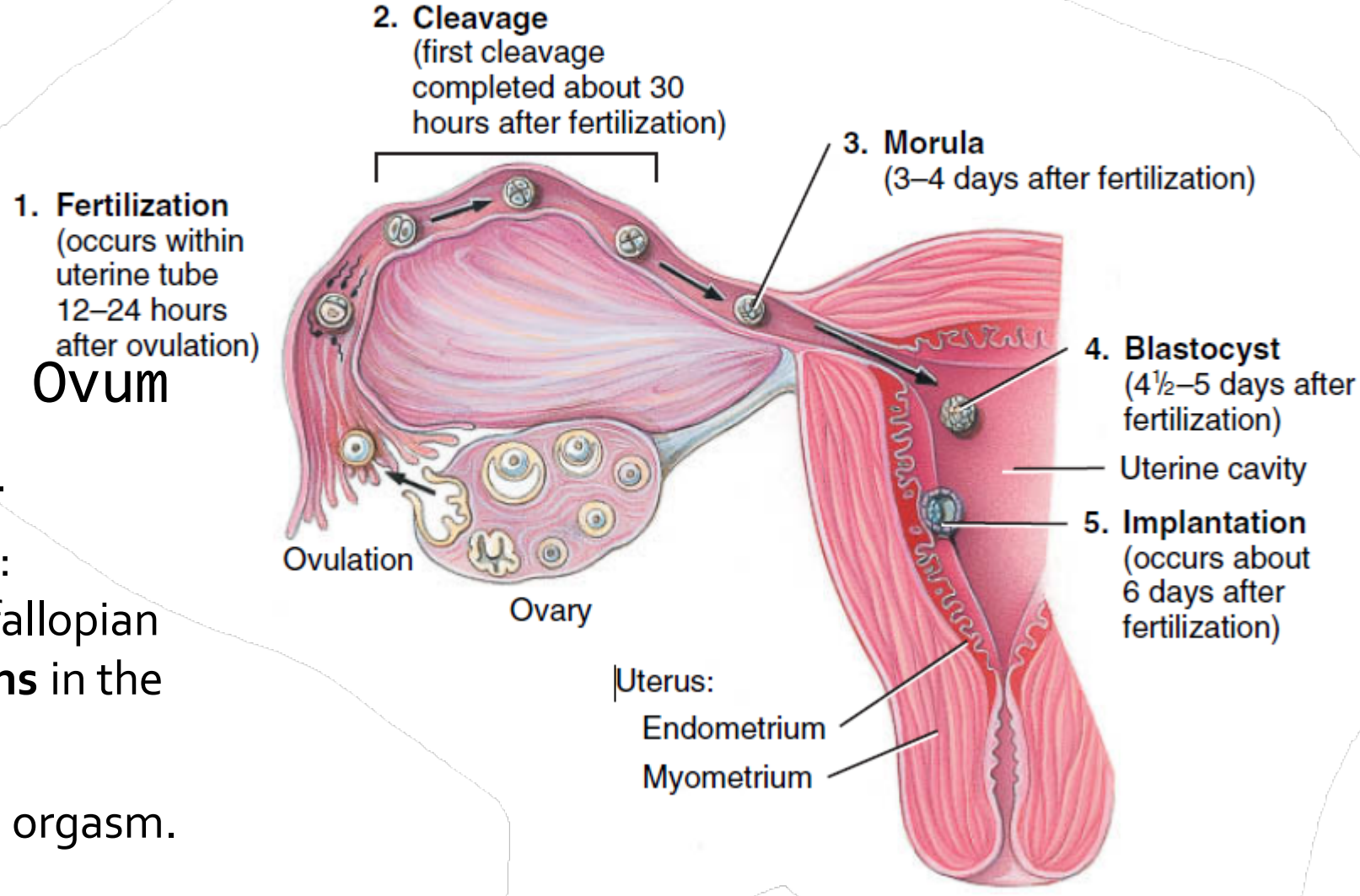
Maturation and Fertilization of the Ovum

Entry of the Ovum into the Fallopian Tube

- Cilia are activated by estrogen.
- 98% success

Fertilization of the Ovum

- At ampullae of the fallopian tubes.
- Transport of the sperm is aided by:
  1.**Contractions** of the uterus and fallopian tubes stimulated by **prostaglandins** in the male seminal fluid.
- 2. **Oxytocin** release during female orgasm.



In previous lectures we learned the process that happens before fertilization :

1. The ovary ovulates and produces an ovum.
2. The fimbrea of the fallopian tube takes the ovum inside with 98% success rate.
3. The reminant of the ovum in the ovary turns into corpus luteum.
4. The ovum is available in the ampulla of the fallopian tube for 12-24 hours for fertilization by the sperm. While the life of sperm is maximum for 72 hours.
5. If there is a living sperm in the ampulla of fallopian tube then ovulation happens, then there is a chance for fertilization, and if there is a living ovum in the fallopian tube then a sperm arrives in this time also fertilization could happen.
6. The overlap between the life of the ovum and the life of the sperm is called the **fertility window,** which is 1 day before ovulation to 2 days after ovulation. So if pregnancy is desired, intercourse should be within this window, if it is not desired, then in other times.
7. In the trip from the fallopian tube to the uterus, the fertilize zygote goes through many division until it becomes a 100 cell blastocyst, this process requires energy and nutrition, for that; the fallopian tubes provides these nutrients through secretions under the influence of hormones released by the corpus luteum.

What aids the sperm to reach the ovum in the ampulla of fallopian tube?

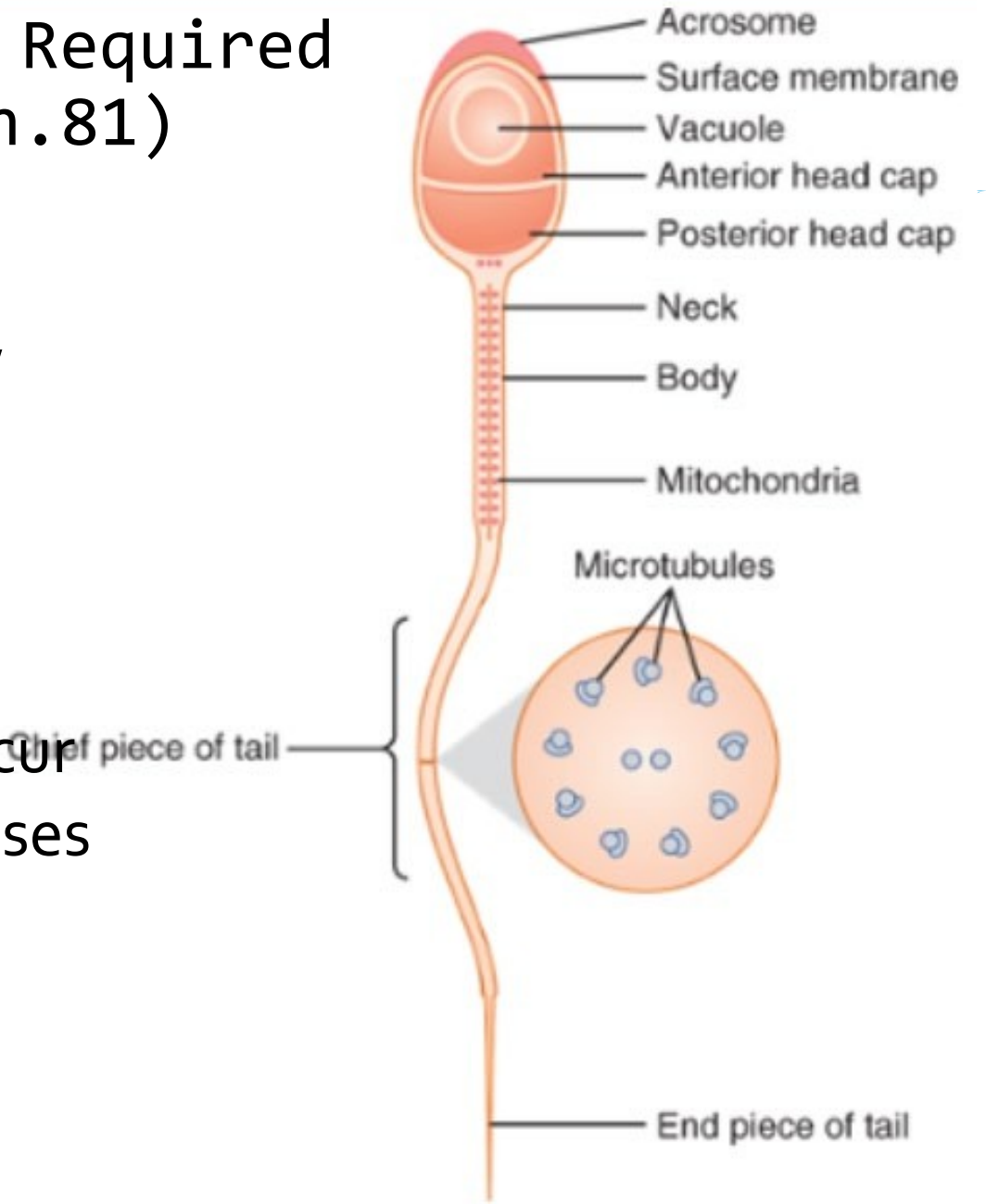
1. The oxytocin released by the female causes contraction in the fallopian tube to help the sperm reach the ampulla.
2. Prostaglandins present in the seminal fluid also causes contractions

NOTES

**The secondary oocyte is ovulated into the abdominal cavity. Then, almost immediately, it enters the fimbriated end of one of the fallopian tubes.
**slow fluid current flowing toward the ostium

"Capacitation" of Spermatozoa Is Required for Fertilization of the Ovum (Ch.81)

- Although spermatozoa are said to be "**mature**" when they leave the **epididymis**, their activity is held in check by **multiple inhibitory factors** secreted by the genital duct epithelia. (unable to fertilize)
- Coming in contact with the **fluids of the female genital tract**, multiple **changes** occur that activate the sperm for the final processes of fertilization.
- These collective changes are called **capacitation** of the spermatozoa (1-10 h)



“Capacitation” of Spermatozoa Is Required for Fertilization of the Ovum (Ch.81)

- 1. Female fluids **wash** away the various **inhibitory factors**.
- 2. Sperms **lose** much of their other **excess cholesterol** → the membrane at the head of the sperm (the acrosome) becomes much weaker.
- 3. The membrane of the sperm also becomes much **more permeable to calcium ions**, so calcium now enters the sperm in abundance and changes the activity of the **flagellum.**
- 4. Calcium ions make it possible for the **acrosome to release its enzymes** rapidly and easily.

In the testis, when the spermatozoa is mature and transported to the epididymis, it gets exposed to inhibitory factors and cholesterol that inhibit motility of the sperm, but without motility the sperm is not able to fertilize the ovum, here comes the role of the female genital tract.

The process of enabling the sperm after entering the female genital tract is called **capacitation**, which takes about 10 hours, and it is facilitated by the fluids of the female genital tract, and they are :

1. Washing away the inhibitory factors
2. Washing away of the cholesterol making the head of the perm weaker to help the release of the acrosome.
3. Making sperm more permeable to calcium, because calcium is necessary for motion of the flagellum , (like any muscle in the body).
4. Also calcium makes an action potential inside the sperm to cause the release of the acrosome.

NOTES

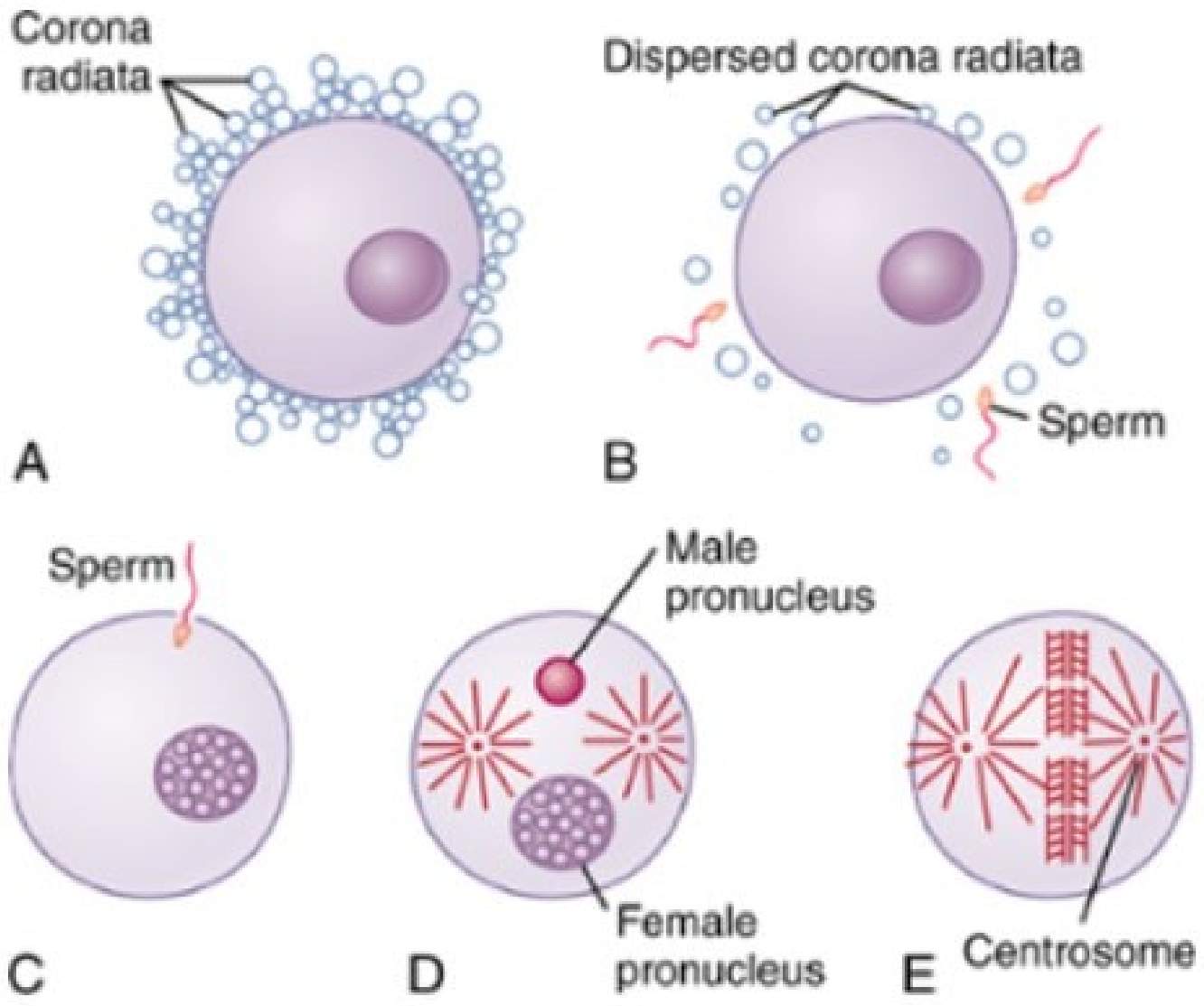
2. While the spermatozoa remain in the fluid of the male genital ducts, they are continually exposed to many floating vesicles from the seminiferous tubules containing large amounts of cholesterol. This cholesterol is continually added to the cellular membrane covering the sperm acrosome, toughening this membrane and preventing release of its enzymes. After ejaculation, the sperm deposited in the vagina swim away from the cholesterol vesicles upward into the uterine cavity, and they gradually lose much of their other excess cholesterol during the next few hours. In so doing, the membrane at the head of the sperm (the acrosome) becomes much weaker.

3+4. The membrane of the sperm also becomes much more permeable to calcium ions, so calcium now enters the sperm in abundance and changes the activity of the flagellum, giving it a powerful whiplash motion in contrast to its previously weak undulating motion. In addition, the calcium ions cause changes in the cellular membrane that cover the leading edge of the acrosome, making it possible for the acrosome to release its enzymes rapidly and easily as the sperm penetrates the granulosa cell mass surrounding the ovum, and even more so as it attempts to penetrate the zona pellucida of the ovum.

Zona pellucida = layer of protoglycans, corona radiata = layer of granulosa cells

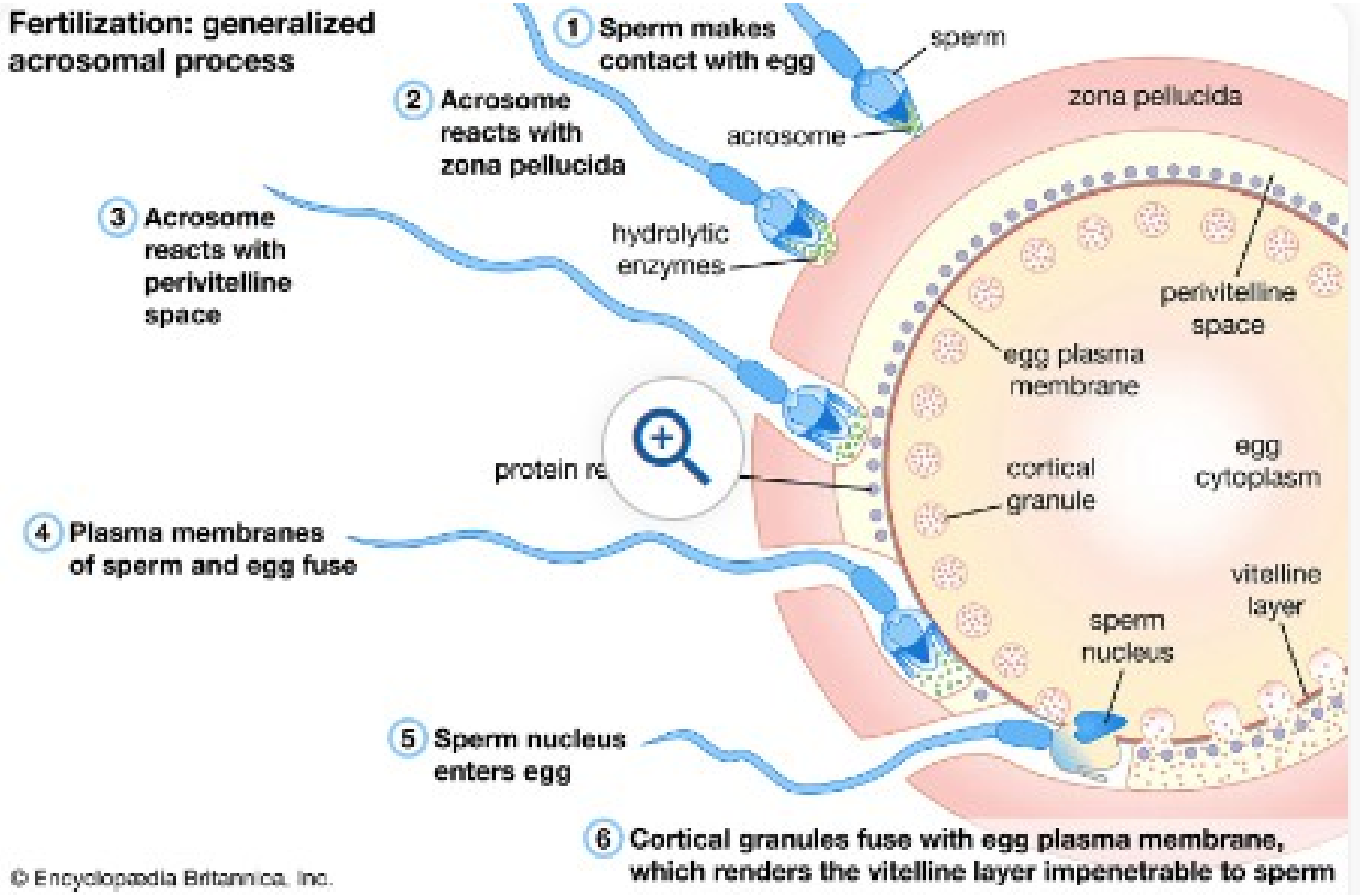
Fertilization of the Ovum

- Sperm penetrates corona radiata and zona pellucida.
- 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
- Fertilized ovum (zygote) contains 23 paired chr (46)



NOTES

**What Determines the Sex of the Fetus That Is Created?


Fertilization: generalized acrosomal process
1 Sperm makes contact with egg
2 Acrosome reacts with zona pellucida
3 Acrosome reacts with perivitelline space
4 Plasma membranes of sperm and egg fuse
5 Sperm nucleus enters egg
6 Cortical granules fuse with egg plasma membrane, which renders the vitelline layer impenetrable to sperm
sperm
acrosome
zona pellucida
hydrolytic enzymes
perivitelline space
egg plasma membrane
cortical granule
egg cytoplasm
vitelline layer
sperm nucleus
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1. After washing off cholesterol, and sperm making contact with zona pellucida (protoglycans) acrosomes release as their hydrolytic enzymes and start digging through the layers.
2. Sperm also digs through the perivetteline space.
3. Sperm fuses with the oocyte and the nuclear material of the sperm enters the the ovum.
4. The fusion of the sperm with the ovum releases cortical granules of the ovum into the perivitteline space, this prevents any other sperm to fuse with the ovum, and if there are any sperm that is trying tho fuse, they will fall off, this prevents polyspermy.

NOTES

Why only one sperm?
within afew minutes after the first sperm penetrates the zona pellucida of the ovum, calcium ions diffuse inward through the oocyte membrane and cause multiple cortical granules to be released by exocytosis from the oocyte into the perivitelline space. These granules contain substances that permeate all portions of the zona pellucida and prevent binding of additional sperm, and they even cause any sperm that have already begun to bind to fall off.

Acrosome Enzymes, the "Acrosome Reaction," and Penetration of the Ovum

- Stored in the **acrosome** of the sperm are large quantities of **hyaluronidase** and **proteolytic enzymes**.

- Hyaluronidase depolymerizes the hyaluronic acid polymers in the **intercellular cement that holds the ovarian granulosa cells together**.

- The proteolytic enzymes **digest proteins in the structural elements** of tissue cells that still adhere to the ovum.

Acrosome Enzymes, the "Acrosome Reaction," and Penetration of the Ovum

- The **anterior membrane** of the sperm binds specifically with **receptor** proteins in the zona pellucida.
- Next, the entire acrosome rapidly dissolves, and **all** the **acrosomal** enzymes are released.
- Within minutes, these enzymes open a **penetrating pathway** for passage of the sperm head through the zona pellucida to the inside of the ovum.
- Within another 30 minutes, the **cell membranes of the sperm head and of the oocyte fuse with each other to form a single cell.**
- At the same time, the **genetic material** of the sperm and the oocyte **combine** to form a completely new cell genome, containing equal numbers of chromosomes and genes from mother and father.

Why Does Only One Sperm Enter the Oocyte?

- Within a **few minutes** after the first sperm penetrates the zona pellucida of the ovum, **calcium ions diffuse inward** through the oocyte membrane and cause **multiple cortical granules** to be released by **exocytosis** from the oocyte into the perivitelline space.

- These granules contain substances that **permeate all portions of the zona pellucida** and prevent binding of additional sperm, and they even cause any sperm that have already begun to bind to fall off.

- # Transport of the Fertilized Ovum in the Fallopian Tube

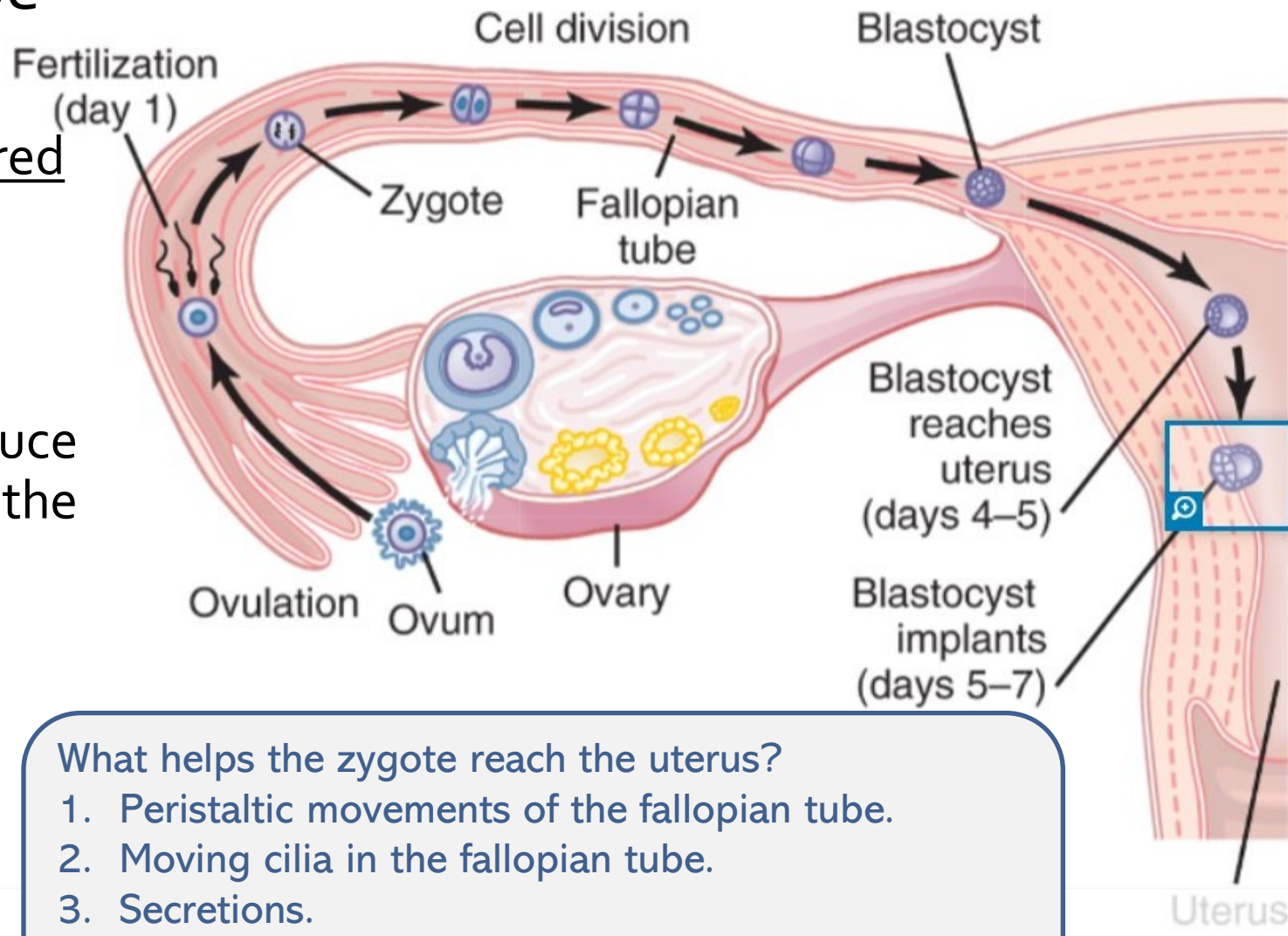
- After fertilization has occurred, an additional 3 to 5 days is normally required for transport of the fertilized ovum through the remainder of the fallopian tube into the cavity of the uterus.

- The fallopian tube secretory cells produce large quantities of secretions used for the nutrition of the developing blastocyst.

- Several stages of cell division occurs, blastocyst, 100 cells.

- **Progesterone** causes relaxation of isthmus.

Isthmus of fallopian tube.



What helps the zygote reach the uterus?

1. Peristaltic movements of the fallopian tube.
2. Moving cilia in the fallopian tube.
3. Secretions.
4. Progesterone which helps relax the isthmus of the fallopian tube.

NOTES

This transport is effected mainly by a feeble **fluid current in the tube resulting from epithelial secretion plus action of the **ciliated epithelium** that lines the tube; the cilia always beat toward the uterus. **Weak contractions** of the fallopian tube may also aid passage of the ovum

**the *isthmus* of the fallopian tube (the last 2 centimeters before the tube enters the uterus) remains spastically contracted for about the first 3 days after ovulation.

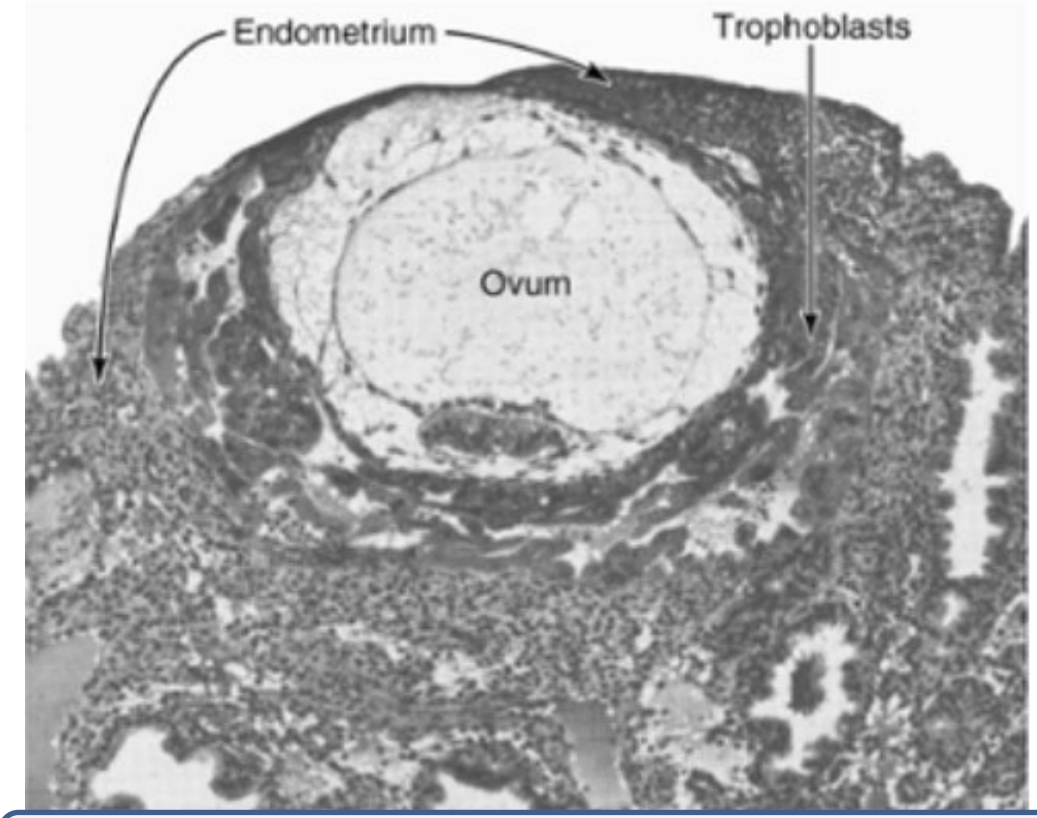
Implantation doesn't happen unless the zygote is a blastocyst (100 cells)

- # Implantation of the Blastocyst in the Uterus

- After reaching the uterus, the developing blastocyst usually remains in the uterine cavity an additional 1 to 3 days before it implants in the endometrium. (**5-7 after ovulation).**

- Before implantation, the blastocyst obtains its nutrition from the uterine endometrial secretions, called **"uterine milk."**

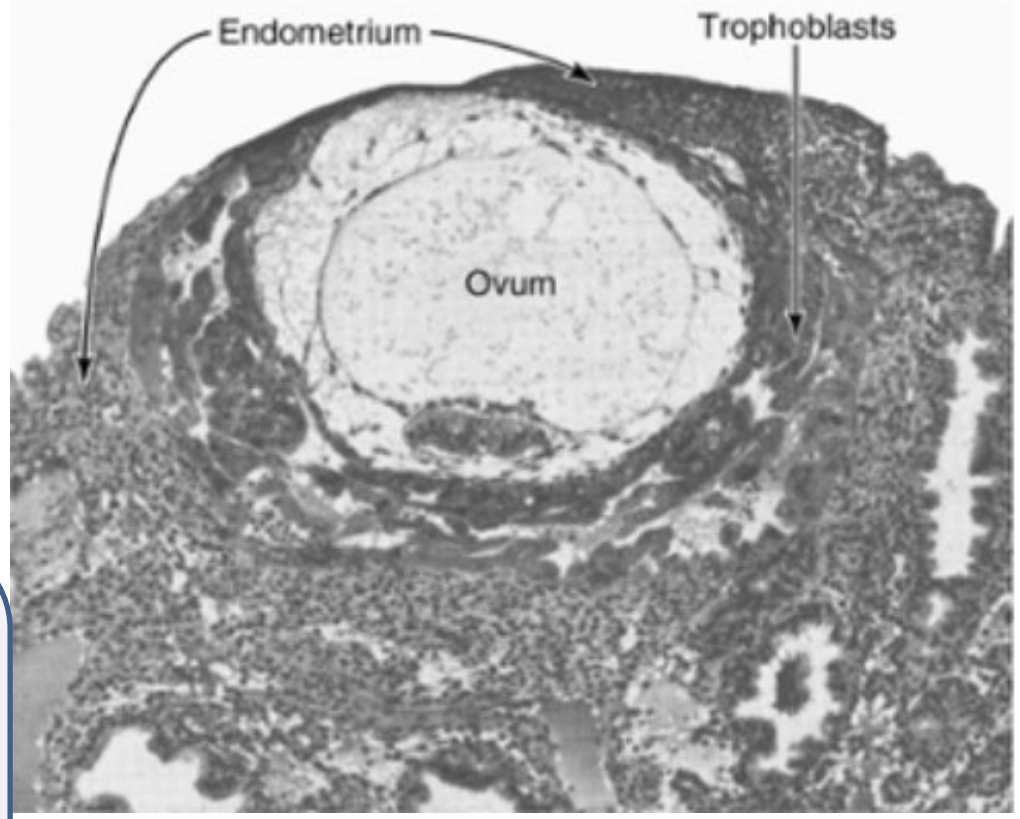
- **Implantation results from the action of trophoblast** cells that develop over the surface of the blastocyst.



Real EM of a zygote implanted in the endometrium

Implantation of the Blastocyst in the Uterus

- Trophoblast secrete proteolytic enzymes that digest and liquefy the adjacent cells of the uterine endometrium.
- Some of the fluid and nutrients released are actively transported by the same trophoblast cells into the blastocyst, adding more sustenance for growth.



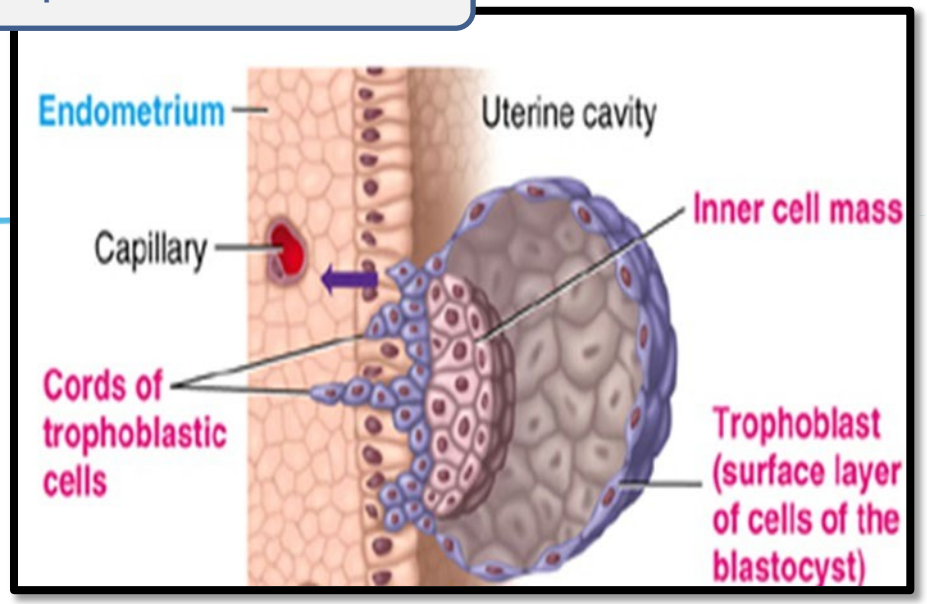
The zygote is surrounded by a layer of cells called the **trophoblast**, it has many functions :

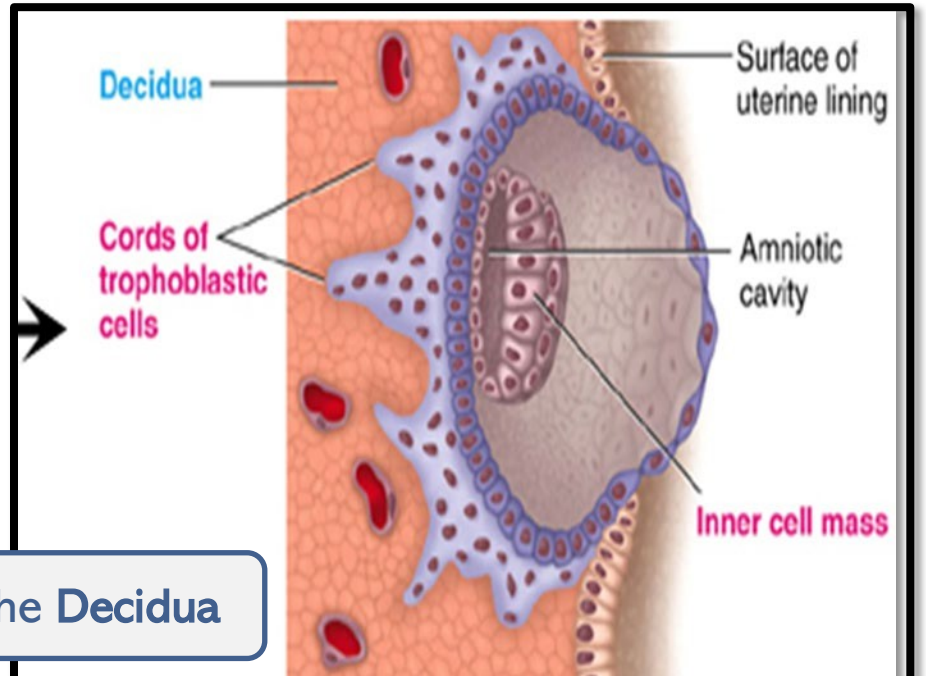
1. Obtaining nutrients (uterine milk) and providing it to the zygote.
2. Releasing proteolytic enzymes to dig through the endometrium for implantation, and using the proteolyzed proteins to provide nutrition for the zygote.
3. After implantation trophoblasts grow roots (cords) in the endometrium to reach blood vessels.

Inner cell mass -> the baby, Trophoblast -> the placenta

Implantation

- The trophoblast cells and other adjacent cells (from the blastocyst and the uterine endometrium) proliferate rapidly, forming the placenta and the various membranes of pregnancy.
- Blood capillaries grow in the trophoblastic cords.
- 21 days after fertilization, blood starts to be pumped by fetal heart into the capillaries.
- Maternal blood sinuses develop around the trophoblastic cords.
- More and more trophoblast projections develop (placental villi).

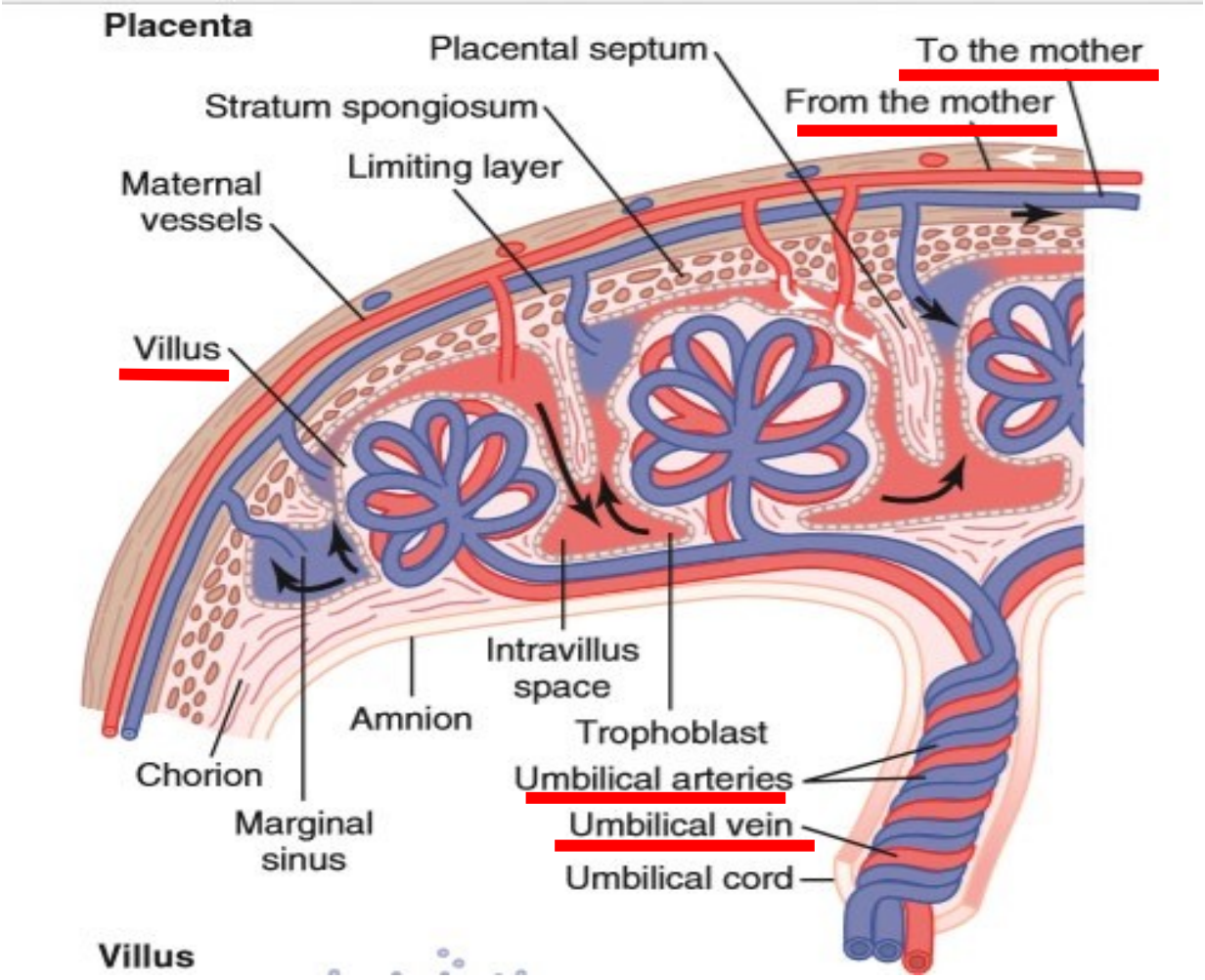




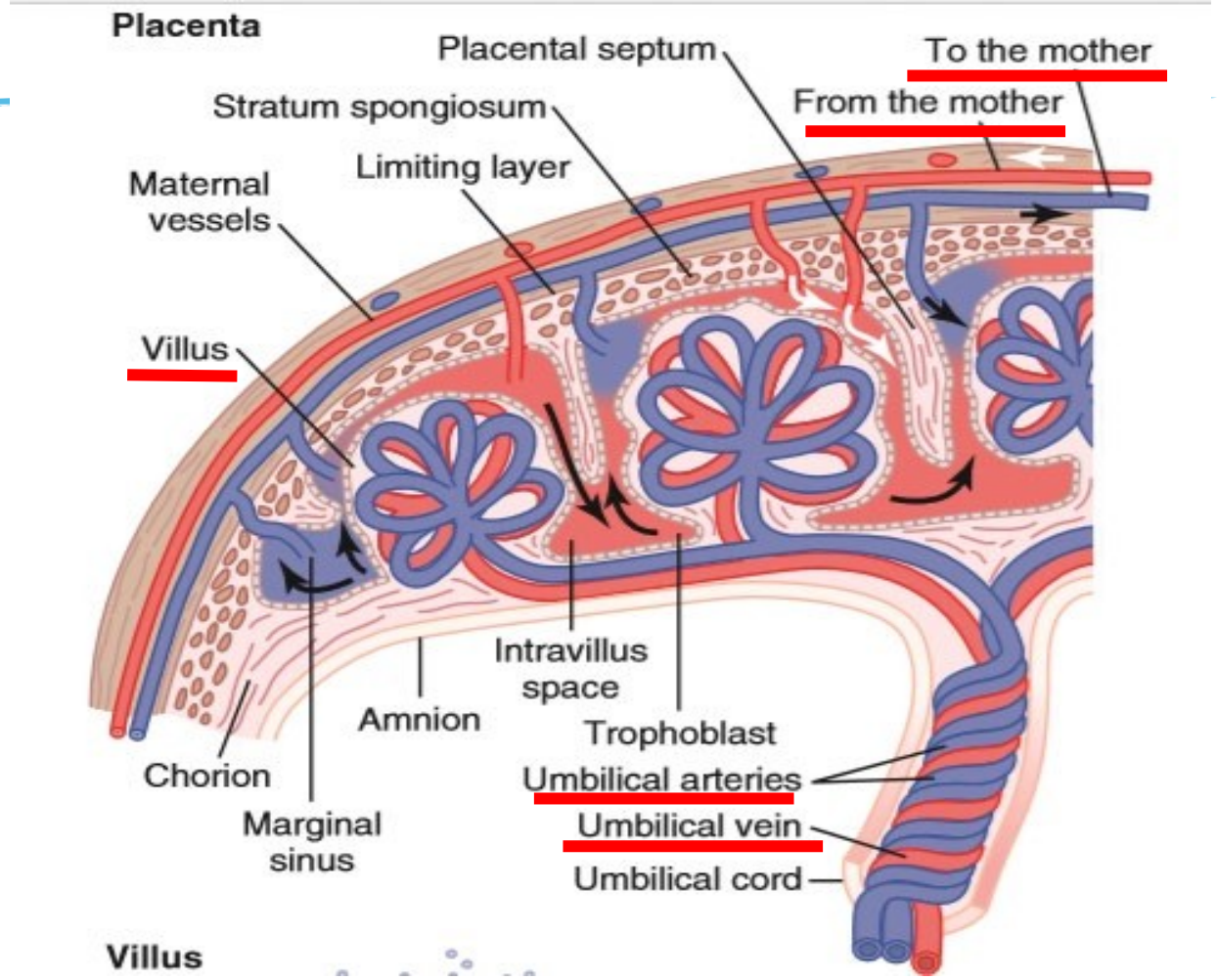
The endometrium where the blastocyst implants differentiate into the **Decidua**

PLACENTA

- Fetus's blood flows through two umbilical arteries, then into the capillaries of the villi.
- Finally back through a single umbilical vein into the fetus.
- At the same time, the mother's blood flows from her uterine arteries into large maternal sinuses that surround the villi and then back into the uterine veins of the mother.



The trophoblastic cords will eventually differentiate into villi which are fetal blood vessels that come in contact with maternal blood sinusoids, but doesn't allow them to mix together. These villi will give rise to 1 umbilical veins and 2 umbilical artery (remember that veins are vessels that go towards the heart and arteries are vessels going out of the heart), the **1 veins carry oxygenated blood and nutrients**, and the 2 artery **carries deoxygenated blood and waste.**

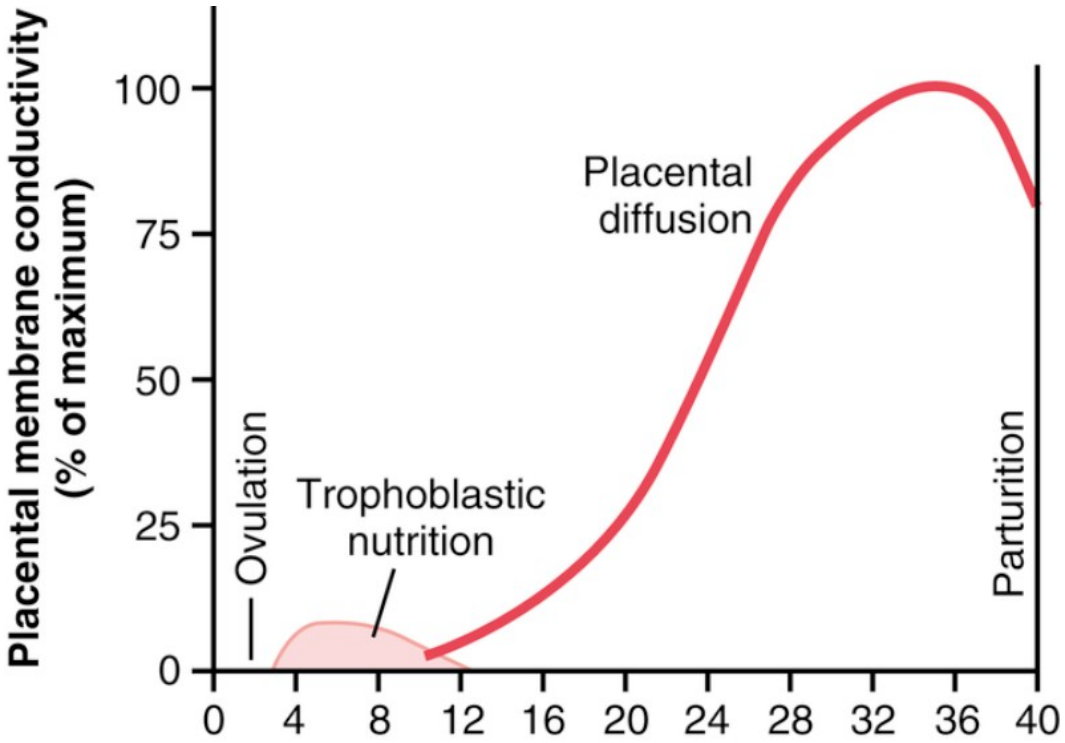


NOTES

**Thus, the villi, carrying fetal blood, are surrounded by sinuses that contain maternal blood.
**he final structure of the placenta, Note that the blood of the fetus flows through two umbilical arteries, then into the capillaries of the villi, and finally back through a single umbilical vein into the fetus. At the same time, the mother's blood flows from her uterine arteries into large maternal sinuses that surround the villi and then back into the uterine veins of the mother.

Early Nutrition of the Embryo

- During the first week after implantation, **decidua** is the **only mean** by which the embryo can obtain nutrients.
- The embryo continues to obtain at least some of its nutrition in this way for up to 8 weeks.
- The placenta also begins to provide nutrition after about the 16th day beyond fertilization (a little more than 1 week after implantation).



The pregnancy is divided into 40 weeks, or 3 trimesters (the trimester is 3 months), through these weeks the mode of nutrition for the fetus changes.
The nutrition of the fetus goes through stages :

1. Right after fertilization, the trophoblasts start providing nutrition for the fetus by obtaining them from uterine milk and secretions, this continues until the 8th week of gestation.
2. At the 16th day the placenta starts forming and start obtaining nutrition from the maternal blood using the villi.
3. Notice that there is an overlap between the trophoblastic stage and the placental stage, so trophoblasts keeps providing nutrition even after a while of forming the placenta.
4. Towards the end of the pregnancy, the fetus gets bigger and demands more nutrition, so the placenta gets thinner to allow more nutrients to pass.

NOTES

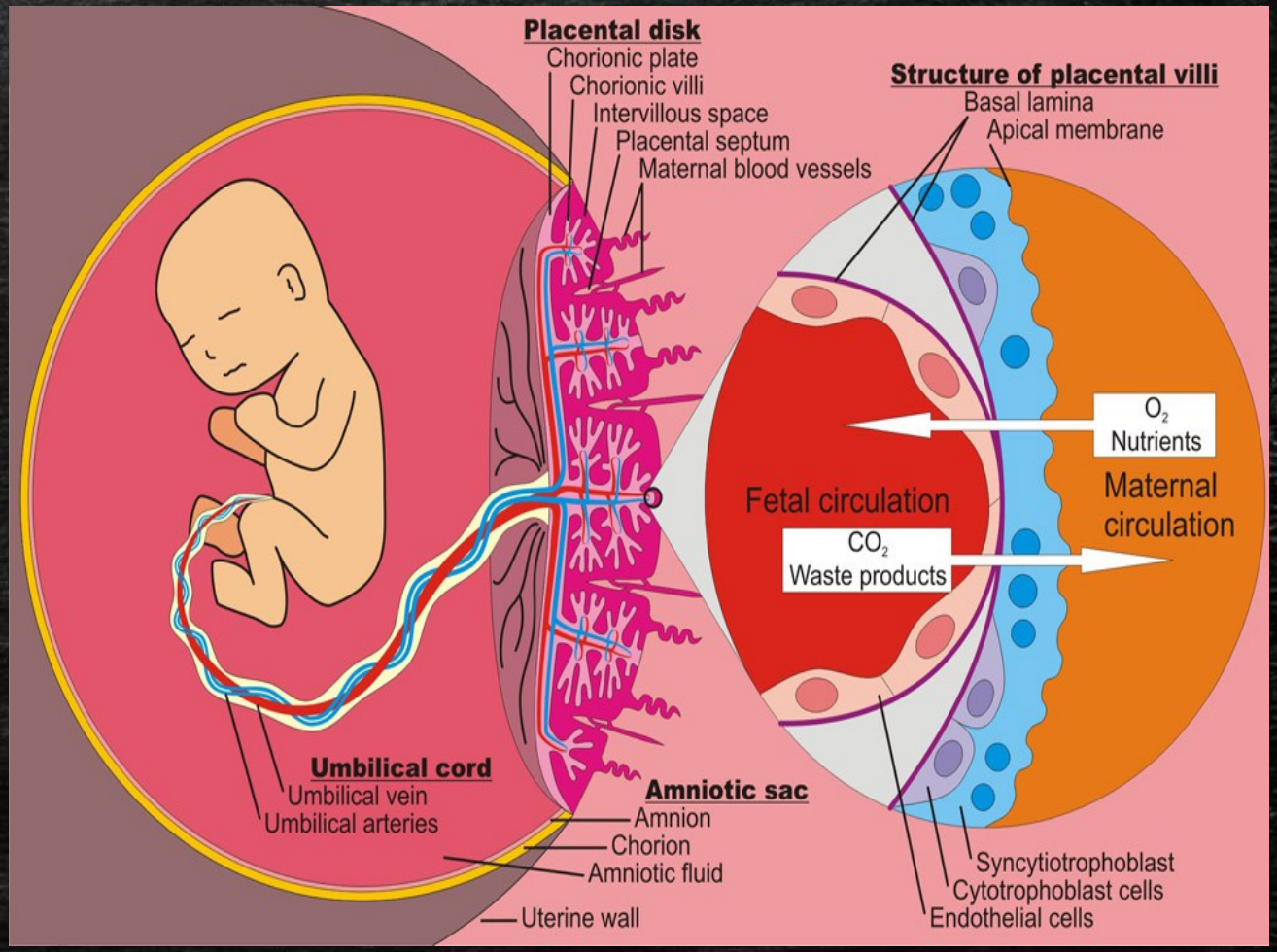
**As the trophoblast cells invade the decidua (endometrial cells), digesting and imbibing it, the stored nutrients in the decidua are used by the embryo for growth and development.
In the early months of pregnancy, the placental membrane is still thick because it is not fully developed. Therefore, its permeability is low. Further, the surface area is small because the placenta has not grown significantly. Therefore, the total diffusion conductance is minuscule at first. 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**

Functions of the placenta

Functions of the placenta

All nutrients are transported through diffusion

- Respiration (simple diffusion)
- Nutrition (facilitated diffusion of glucose)
- Excretion
- Endocrine
- Protection



NOTES

****simple diffusion**, driven by an oxygen pressure gradient from the mother's blood to the fetus's blood

Diffusion of Oxygen Through the Placental Membrane

- Near the end of pregnancy, the mean partial pressure of oxygen (PO 2) of the mother's blood in the placental sinuses is about 50 mm Hg, and the mean PO 2 in the fetal blood after it becomes oxygenated in the placenta is about 30 mm Hg.

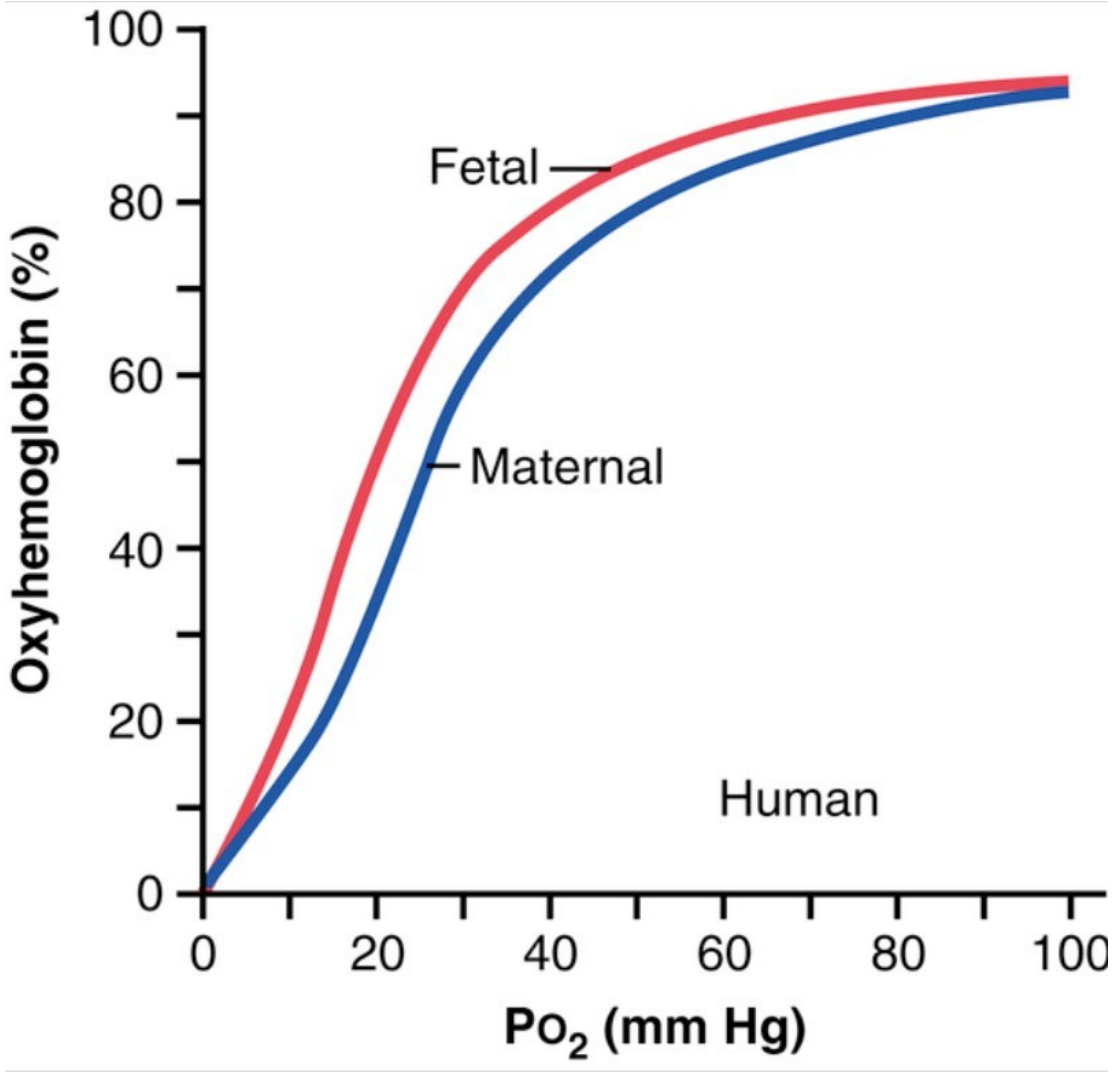
- Therefore, the mean pressure gradient for diffusion of oxygen through the placental membrane is about 20 mm Hg.

Is that enough Oxygen?

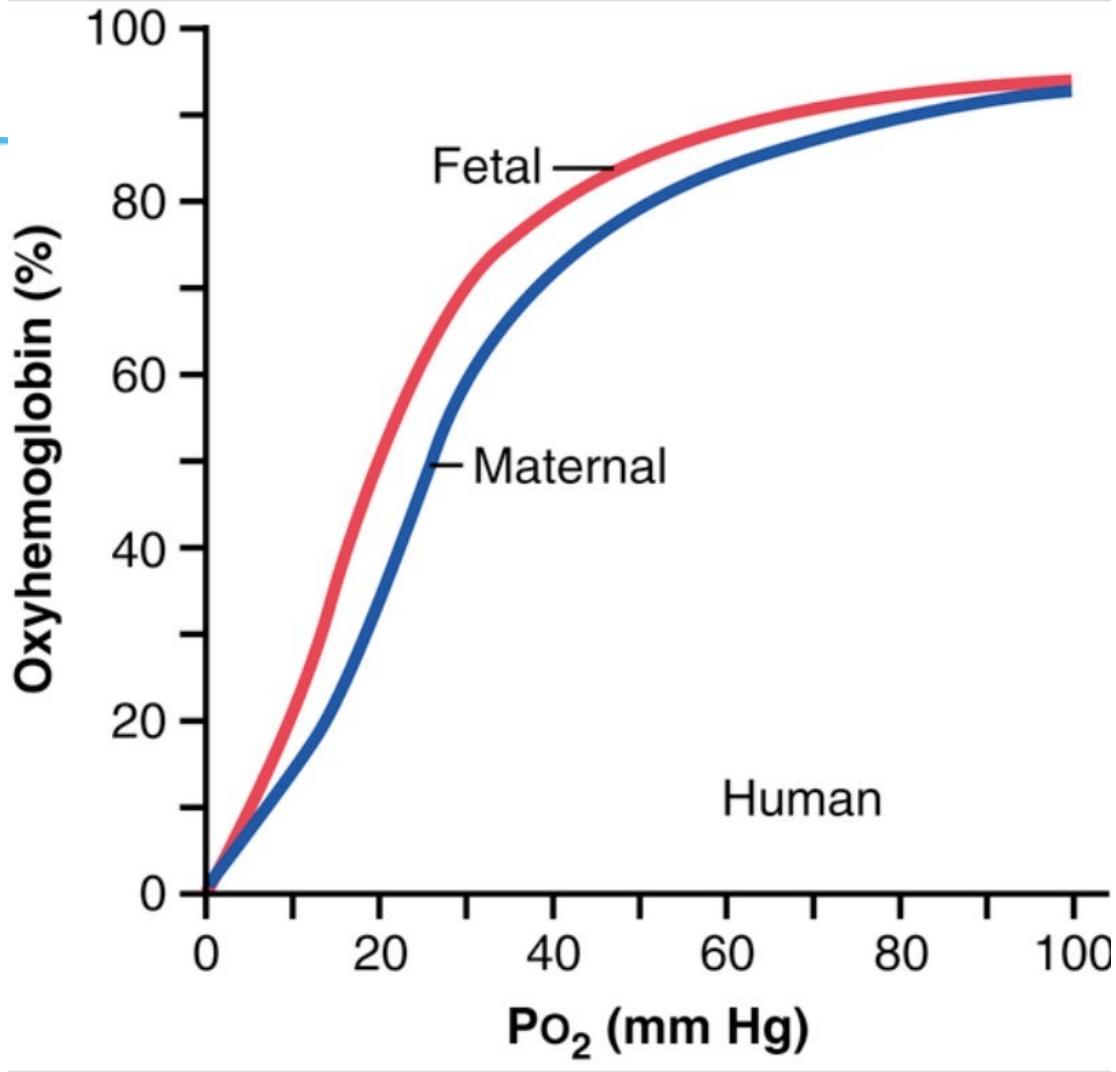
The 20 mmHg pressure difference alone is not enough.

Diffusion of Oxygen Through the Placental Membrane

- The curve for fetal hemoglobin is shifted to the left of that for maternal hemoglobin. This means that at the low PO 2 levels in fetal blood, the fetal hemoglobin can carry 20% to 50% more oxygen than can maternal hemoglobin.
- Hemoglobin concentration of fetal blood is about 50% greater than that of the mother.



Recall HLS biochemistry, we know that fetal hemoglobin has more affinity for oxygen than maternal adult hemoglobin, so this higher affinity pulls more oxygen to the fetal blood, and this adds another factor favoring the diffusion of oxygen from maternal blood towards fetal alongside the 20mmHg pressure difference we mentioned earlier. According to the graph, fetal hemoglobin has left shifting.



NOTES

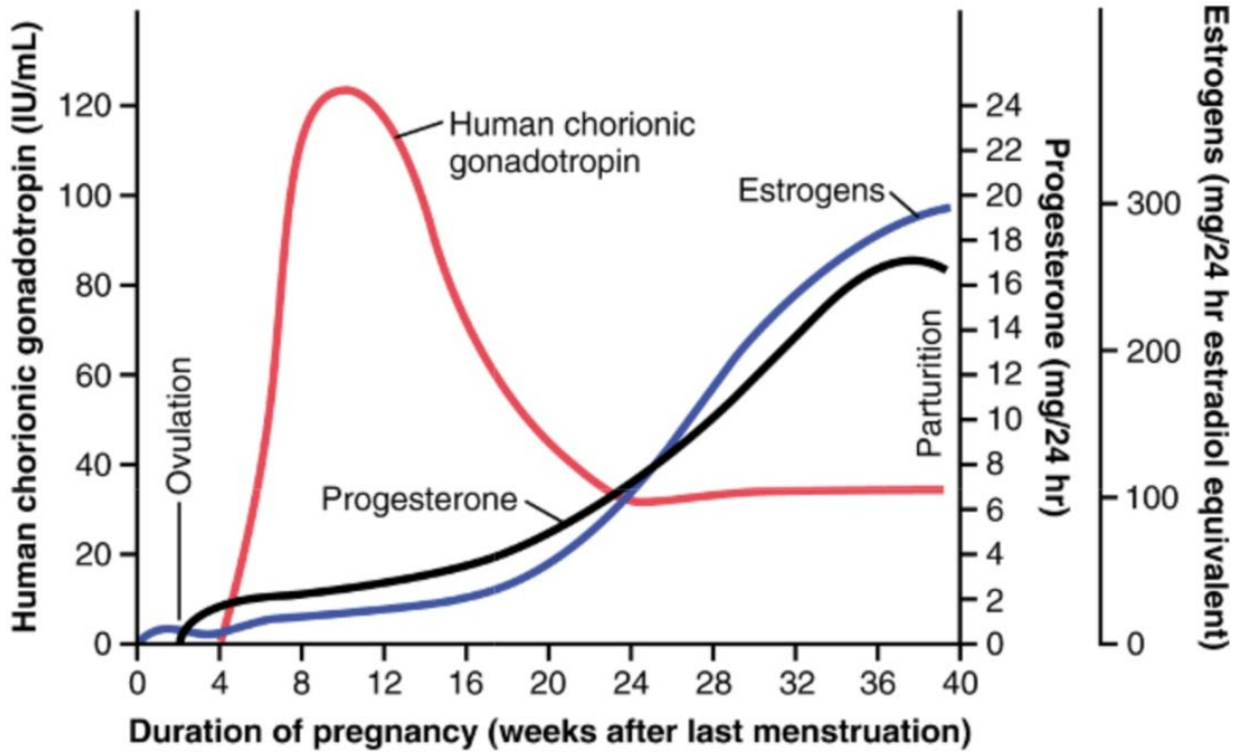
1: the hemoglobin of the fetus is mainly *fetal hemoglobin,* a type of hemoglobin synthesized in the fetus before birth
At lower PO2 this hemoglobin is able to carry more o2 than maternal hemoglobin
3: Bohr effect: hemoglobin can carry more oxygen at a low Pco2 than it can at a high Pco2. when fetal blood clears co2 into maternal blood it will become alkaline and increases affinity to oxygen

Hormonal Factors in Pregnancy

Pregnancy hormones

- In pregnancy, the placenta forms especially large quantities of
  - human chorionic gonadotropin,
  - estrogens,
  - progesterone.

HCG gets lower at the 24th week and then stays constant, while progesterone and estrogen rise in this period.

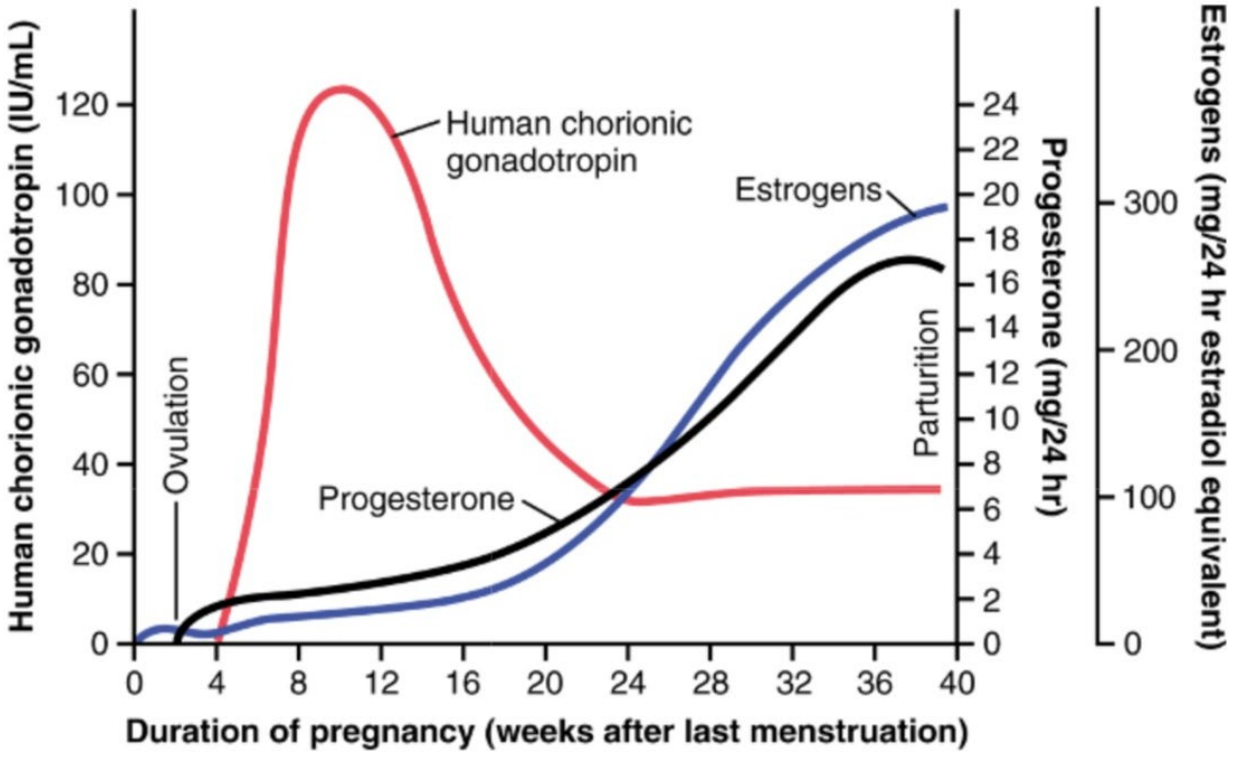


Dr. Read the whole slide.

HCG is what we look for in pregnancy tests

Human Chorionic Gonadotropin (HCG)

- Synthesized by trophoblast cells and secreted into the fluids of the mother.
- Can be measured in the blood 8 to 9 days after ovulation.
- Reach a maximum at about 10 to 12 weeks of pregnancy and decreases back to a lower value by 16 to 20 weeks.
- It continues at this level for the remainder of the pregnancy.



Human Chorionic Gonadotropin (HCG)

- Much similar molecular structure and function as luteinizing hormone.
- Prevents involution of the corpus luteum at the end of the monthly female sexual cycle.
- CL continued secretion of estrogens and progesterone maintains the decidual nature of the uterine endometrium
- CL involutes slowly after the 13th to 17th week of gestation and placenta takes over to secrete estrogen and progesterone
- Stimulates testes of the male fetus to produce testosterone until the time of birth. (grow male sex organs)

- Function as LH for the mother: as we learned before, LH is what stimulates corpus luteum to secrete progesterone (and estrogen), but progesterone has a negative feedback on the secretion of LH, so how can we keep the secretion of progesterone in the absence of LH? Here comes the role of HCG as it acts as LH.
- Function as LH for the baby boy: as we know, for the fetus to differentiate into male, it needs testosterone, and testosterone is only secreted by leydig cells, and they need LH to do that, here also HCG acts as LH for the fetal leydig cells to produce testosterone.

NOTES

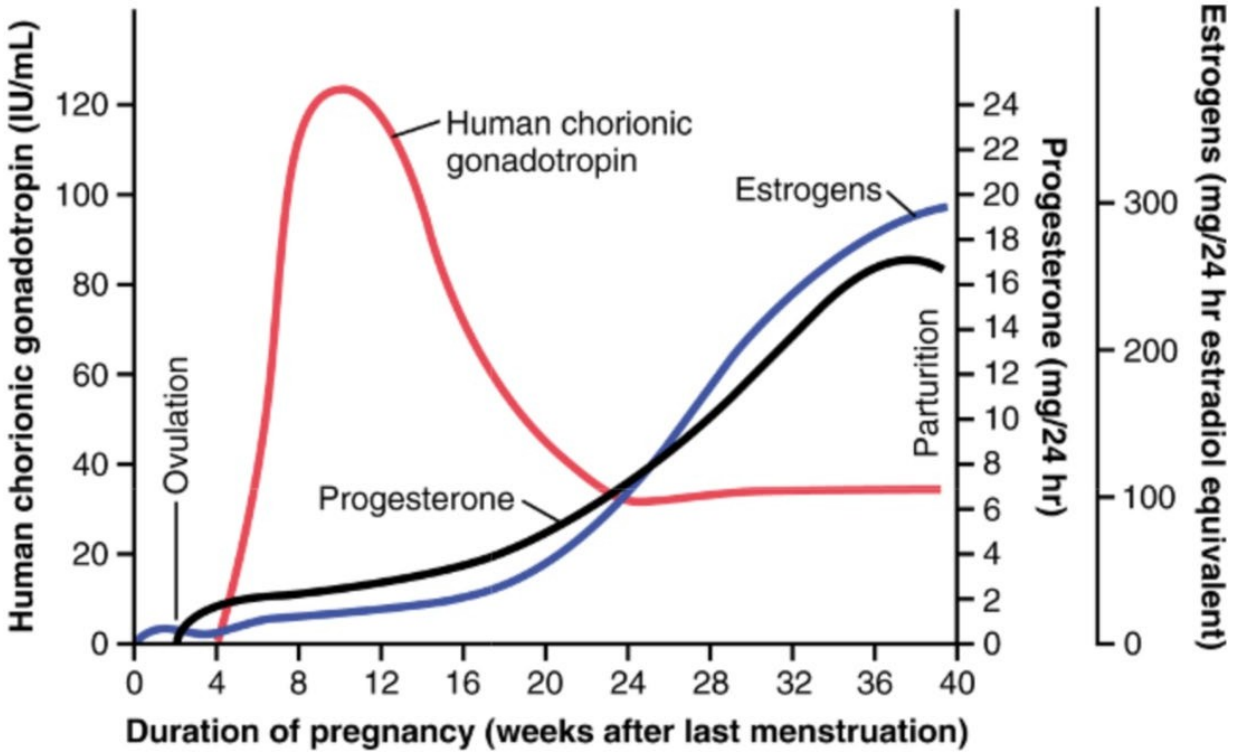
Under the influence of human chorionic gonadotropin,the corpus luteum in the mother’s ovary grows to about twice its initial size by a month or so after pregnancy begins. Its continued secretion of estrogens and progesterone maintains the decidual nature of the uterine endometrium, which is necessary for the early development of the fetus.

Estrogen

More details in slide 46

- Secreted by syncytial trophoblast cells of placenta
- Towards the end of pregnancy it reaches 30×
- Derived from weak androgen (DHEA) released from maternal & fetal adrenals cortex

- Functions in the mother
- Enlargement of uterus, breast (and ductal) & external genitalia
- Relaxation of pelvic ligaments in preparation for labor(sacroiliac joints, symphysis pubis)



NOTES

The placenta converts the androgen hormone produced by the fetal adrenal cortex, dehydroepiandrosterone (DHEA), into estrogen.

** The placenta cannot produce estrogen until the fetus has developed to the point that its adrenal cortex is secreting DHEA into the blood. The placenta extracts DHEA from the fetal blood and converts it into estrogen, which it then secretes into the maternal blood.

Progesterone

More details in slide 46

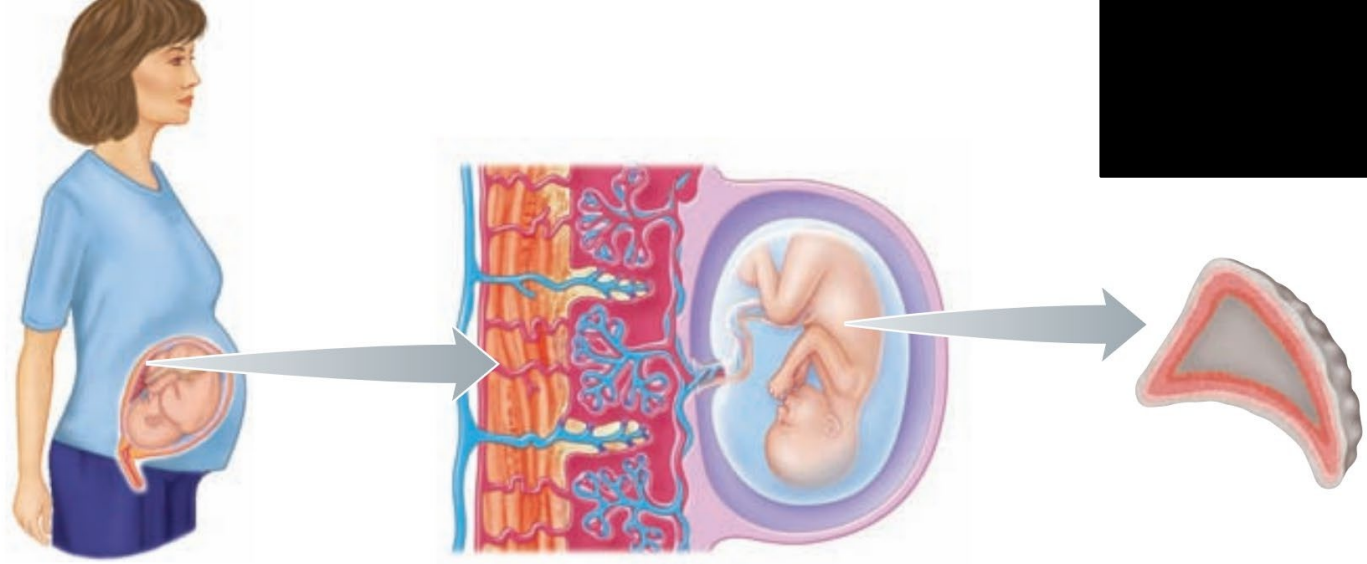
- Progesterone is essential for a successful pregnancy;
- Moderate quantities by the corpus luteum at the beginning of pregnancy
- later in large quantities by the placenta(10X), by syncytial trophoblast cells from cholesterol.
- Effects of progesterone in pregnancy:
- 1. Progesterone causes decidual cells development (nutrition of the early embryo)
- 2. Progesterone decreases the contractility of the pregnant uterus
- 3. Progesterone increases secretions of the mother's fallopian tubes and uterus.
- 4. Prepare the mother's breasts for lactation

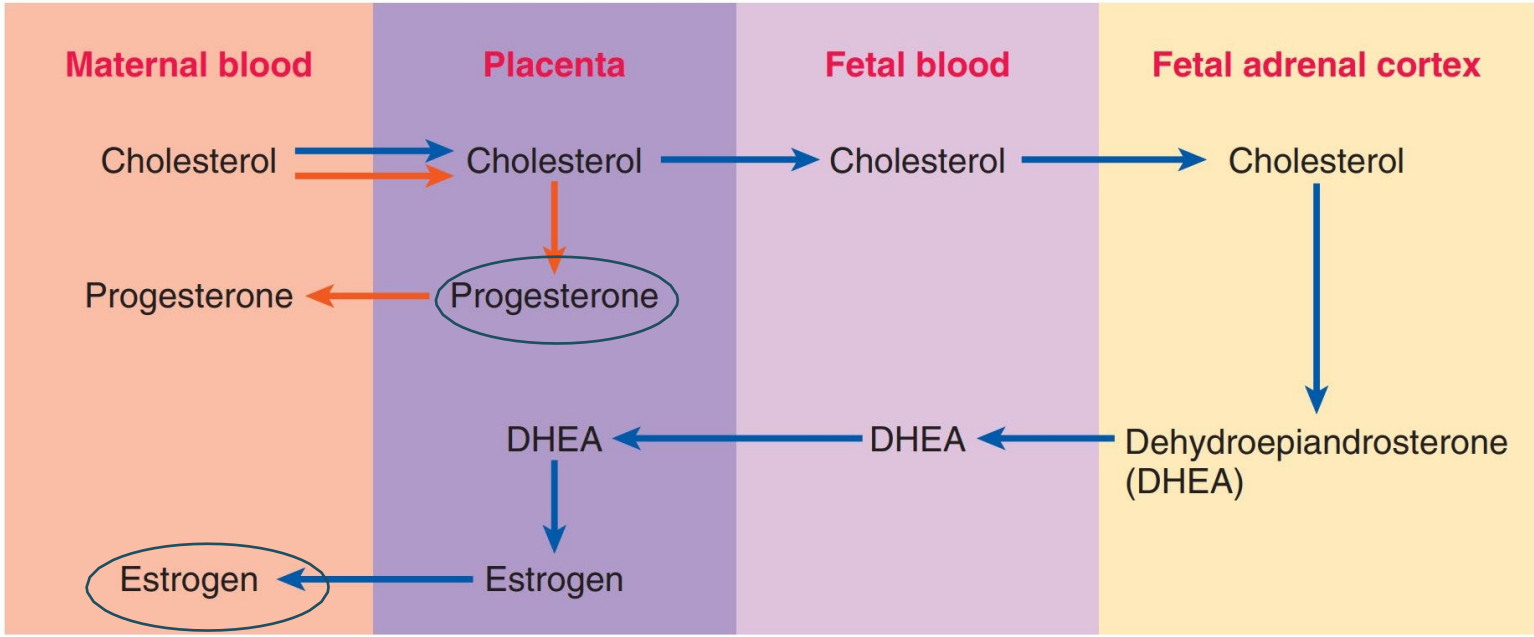
The function of estrogen and progesterone :

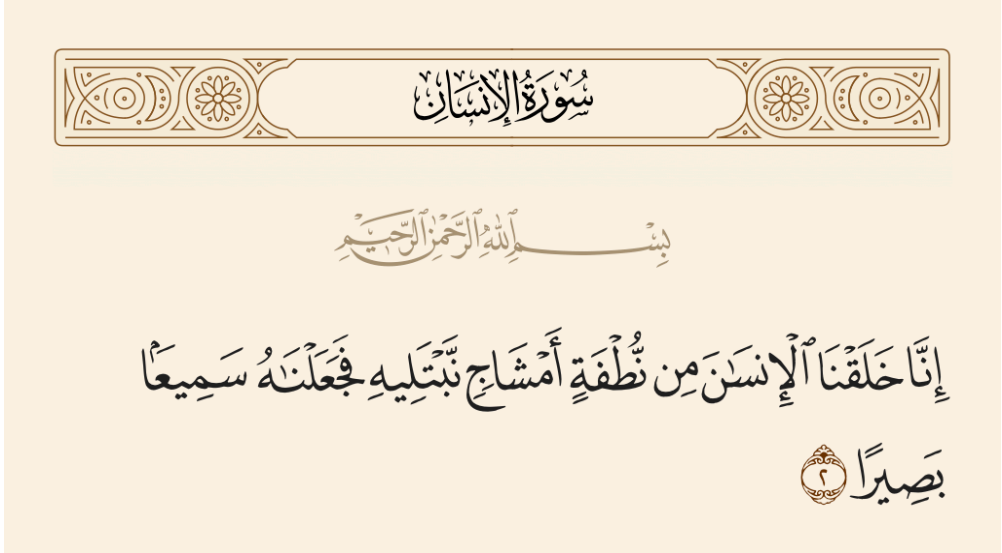
- At the beginning of pregnancy, the ratio of progesterone to estrogen is bigger, this reduces uterine contractions and increases fallopian secretions, alongside other physiologic changes that favor the continuation of pregnancy.
- Later in pregnancy, and specifically at 24 weeks, both progesterone and estrogen rise but now estrogen to progesterone ratio is bigger, this increases the size of uterus, breast, and external genitalia to prepare the body for birth.
- In the earlier stage where progesterone ratio is higher, the production of hormones depends solely on the mother, but in the later stage when estrogen ration is higher, the fetus has a well developed adrenal cortex, so it helps in the **production of DHEA** a precursor for estrogen, so it participates in the preparation for its own birth.

	Ratio	Fetal production	Function
Progesterone	It is higher in the first half of pregnancy but then estrogen takes over	Not produced in the fetus, nor its precursor	Maintaining pregnancy and preventing preterm labour, it also prepares for lactation
Estrogen	It is lower in the first half of pregnancy but then it takes over	At the 24^{th} week when the fetal adrenal cortex is well developed, it starts producing DHEA, an estrogen precursor	Preparing for labour and lactation

As we see here, cholesterol diffuses through the placenta to the fetus so it can produce DHEA, then DHEA goes back to the mother to make estrogen.







VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	24		Please read the paragraph carefully 2 arteries (carry deoxygenated blood) 1 vein (carry oxygenated blood)
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!