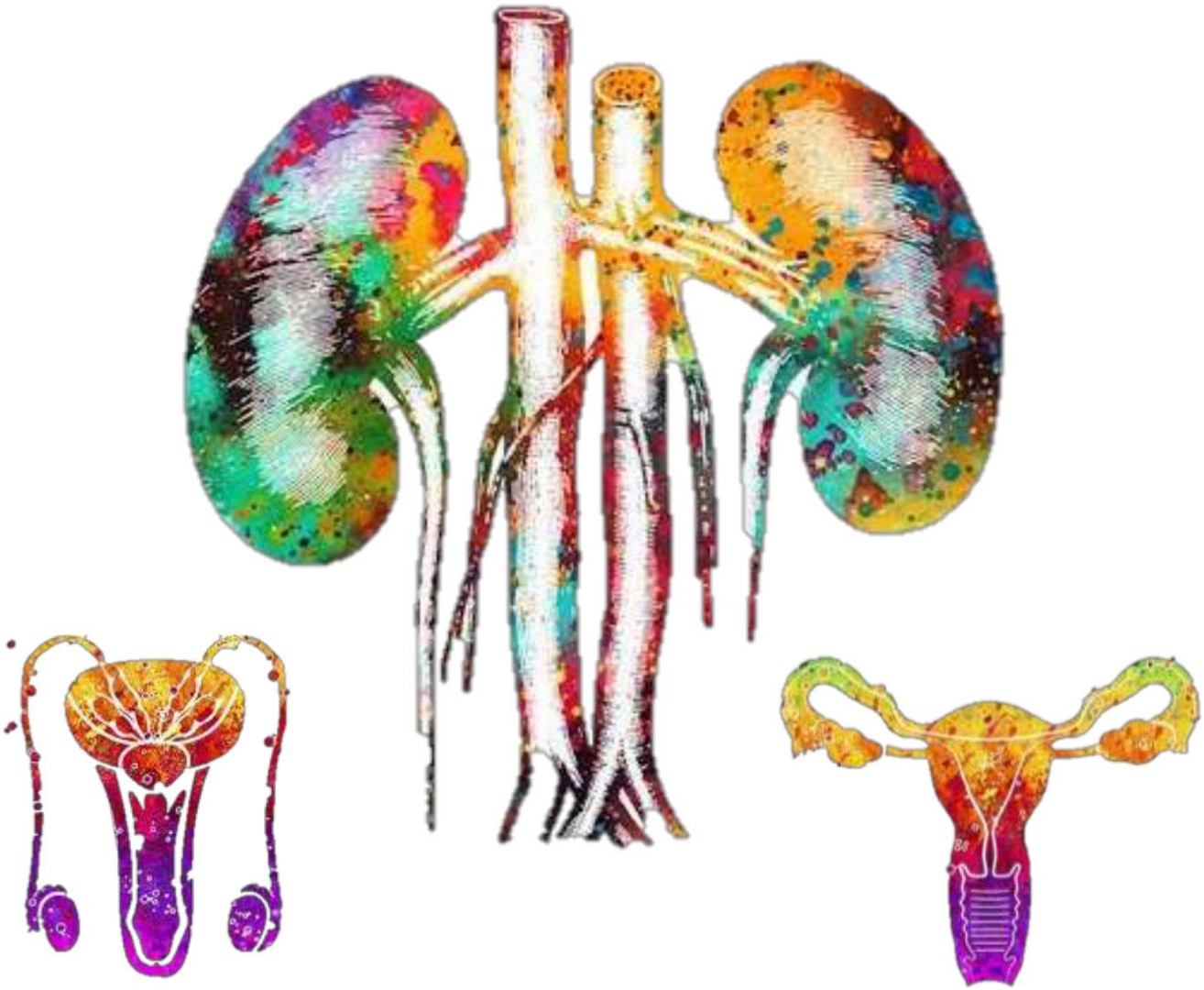

Genitourinary System

Subsystem: Physiology – Lecture 13 (Repro #5)

Lecture Title: Fertilisation & Pregnancy

Lecture Date: 10/5/2020

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Editor: Sima Shihab

- ✓ Sheet corrections link: bit.ly/GUSphysio

Objectives :

- Fertilization
- Development and function of the placenta
- Placenta as an endocrine organ
- Physiological functions of placental hormones
- Maternal adaptation to pregnancy

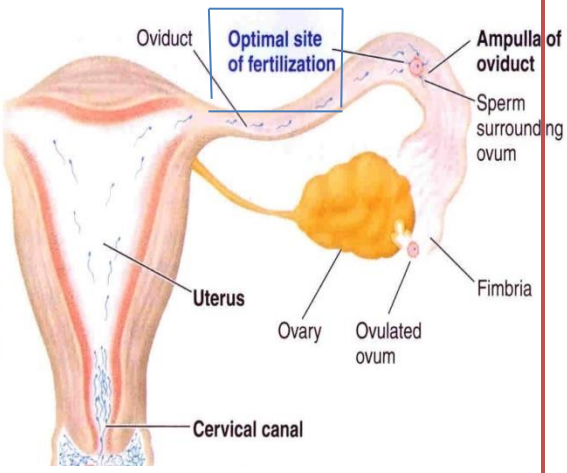
Quick review : OVULATION

Primary oocyte(in the ovary) → before it release from ovarian follicle – meiotic division → secondary oocyte(23 unpaired chromosomes) → ovulated in the peritoneal cavity (Ovum with granulosa cells (corona radiata)) → the movements of the fimbriae help in receiving the released egg and guide it to the fallopian tube

Fertilization :

- Ova can sometimes enter the opposite fallopian tube for one reason or another.
- Fertilization takes place normally in the ampulla
- Transport of sperms aided by **uterine and fallopian tube contraction** stimulated by prostaglandin in the male seminal fluid and oxytocin from posterior pituitary of the female during orgasm.

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



- After ejaculation ; sperms reach ampulla of fallopian tube within 30-60 min (uterine contraction)
- Sperm penetrate corona radiata and zona pellucida that surrounding the ova (via hyaluronidase- Stored in the acrosome of the sperm)
- Once a sperm has entered the ovum (which is still in the secondary oocyte stage of development), the Oocyte divides to form mature ovum (female pronucleus 23 unpaired chromosome) + 2nd polar body

- Head of sperm swells (male pronucleus 23 unpaired chromosome)
- 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

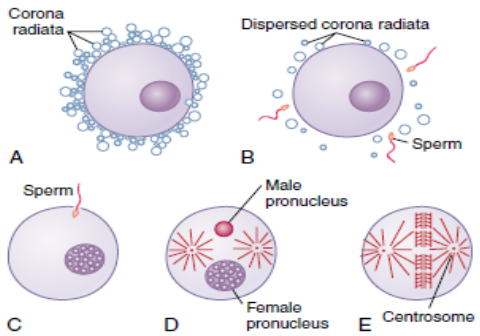
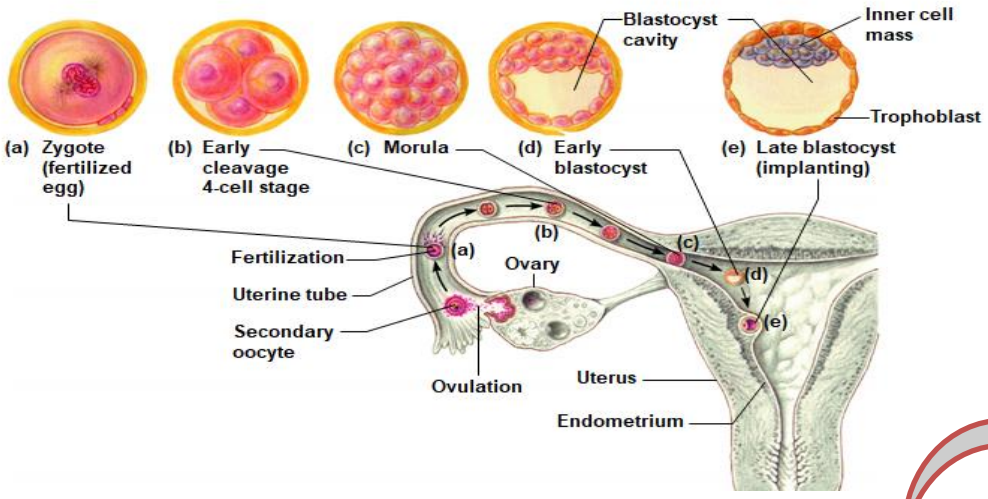


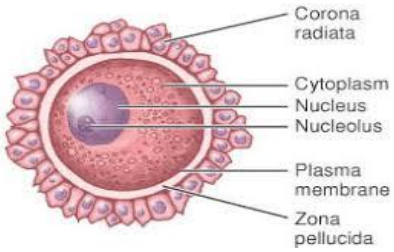
Figure 82-1 Fertilization of the ovum. *A*, The mature ovum surrounded by the corona radiata. *B*, Dispersal of the corona radiata. *C*, Entry of the sperm. *D*, Formation of the male and female pronuclei. *E*, Reorganization of a full complement of chromosomes and beginning division of the ovum. (Modified from Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, 7th ed. Philadelphia: WB Saunders, 1974.)

Cleavage :



sex of the fetus :

1) SPERM **X** OR **Y**
2) OVUM **X** only
3) Male FETUS **XY**
4) FEMALE FETUS **XX**

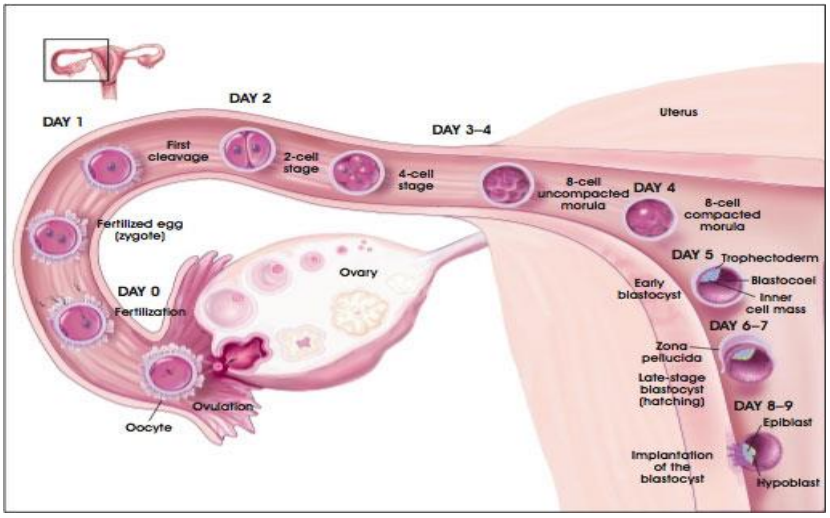


ZONA PELLUCIDA

the thick transparent membrane surrounding a mammalian ovum before implantation.

- In embryology, **cleavage** is the division of cells in the early embryo.
- Following fertilization the zygote undergoes several mitotic divisions inside the zona pellucida (overall size does not change).
- 1st cleavage yields a 2 celled embryo (each cell is called a blastomere)
- Divisions continue rapidly until the 32 cell stage

Transport of fertilized ovum

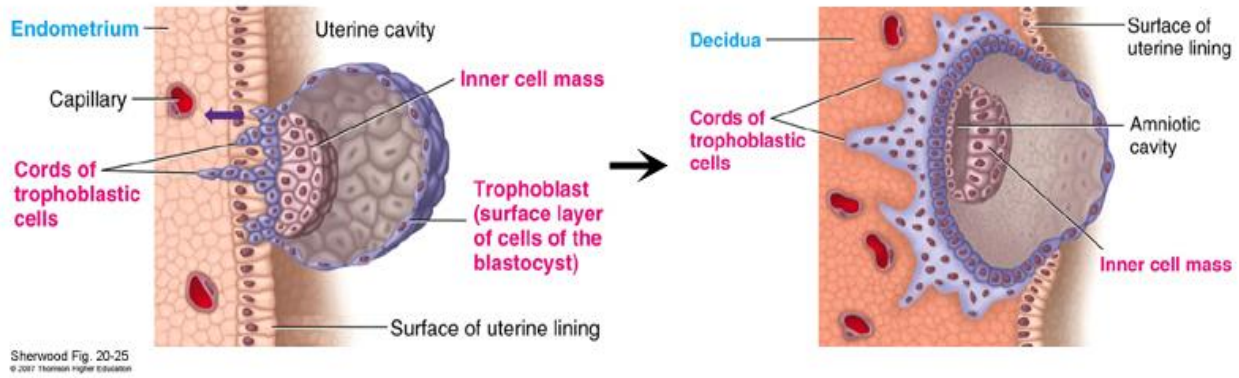


- After fertilization **3-5 days** till zygote reach **uterine cavity**
- Transport: fluid current + action of cilia + weak contractions of the fallopian tube and the isthmus (last 2cm of fallopian tube) **remains contracted for about 3 days after ovulation then isthmus relaxes under effect of progesterone** secrete by the corpus luteum to allows the **entry of the ovum in the uterus**
- Delayed transport allows cell division
- Blastocyst (**100 cells**) enters the uterus

The **blastocyst** is a structure formed in the early development of mammals. It possesses **an inner cell mass (ICM)** which subsequently **forms the embryo**. The **outer layer** of the **blastocyst** consists of cells collectively called the **trophoblast.**

Trophoblasts : are cells that form the outer layer of a blastocyst and are present four days post fertilization in humans. They provide nutrients to the embryo and develop into a large part of the placenta.

Implantation



- The blastocyst **remains 3 days in the uterus** before it's implanted. So, **implantation** occurs about **5th-7th** day after ovulation.
- **Before** implantation the blastocyst obtains nutrition from the endometrial secretion called (UTERINE MILK)
- **Trophoblast** that develop over the blastocyst secrete proteolytic enzymes that **digest** and liquefy the adjacent cells of the endometrium
- Once the implantation takes place the trophoblast, blastocyst and the uterine endometrium **proliferate rapidly** forming the placenta

EARLY NUTRITION OF THE EMBRYO

1- **Progesterone** converts the endometrial **stromal cells into large swollen cells** containing large amounts of glycogen, protein and lipid necessary for development of the embryo.
2- When the Embryo implants into the endometrium, continued secretion of progesterone causes the endometrial cells to swell more; these cells are now called **decidual** cells and the **total** cells called **decidua**
3- The **trophoblast cells** **invade the decidua**, and the stored nutrients in the decidua are now used for the growth & development of the embryo
4- this is the **main feeding process during the first week** and continues as **partial for the next 8 weeks in addition to the placenta**
5- the placenta starts to provide nutrition **after 16 days from fertilization** (little more than **one week after implantation).**

- **Placenta :**

- While the **trophoblastic cords** from the blastocyst are **attaching to the uterus**, blood **capillaries grow into the cords** from the vascular system of the newly forming embryo. About **21 days after fertilization, blood also begins to be pumped by the heart of the human embryo**
- **Maternal blood sinuses develop around the trophoblastic cords**
- The **trophoblast cells send out more and more projections**, which become **placental villi** into which fetal capillaries grow. Thus, the **villi**, carrying fetal blood, are **surrounded** by **sinuses** that **contain maternal blood**.
- **There are two umbilical arteries and one umbilical vein;** the fetus's blood 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
- **<u>Fetal blood can carry a greater quantity of O2 than can maternal blood</u>**

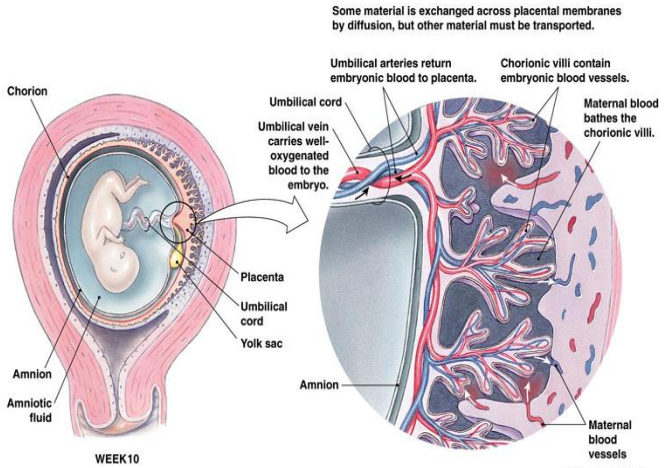


Fig. 26-19

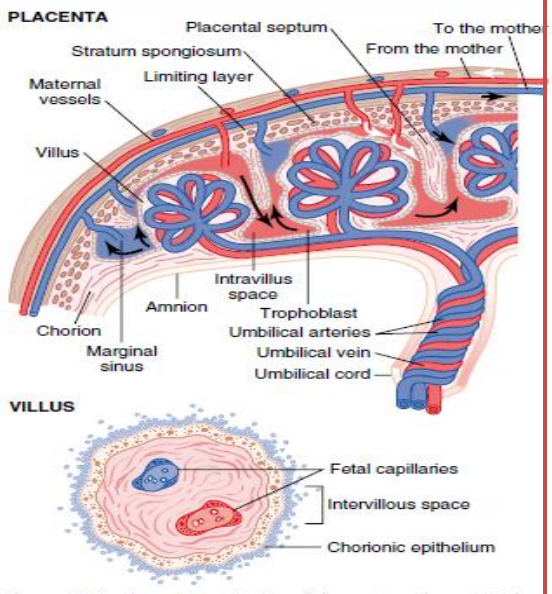


Figure 82-5 *Above*, Organization of the mature placenta. *Below* Relation of the fetal blood in the villus capillaries to the mother's blood in the intervillous spaces. (Modified from Gray H, Goss CM: Anatomy of the Human Body, 25th ed. Philadelphia: Lea & Febiger, 1948; and from Arey LB: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, 7th ed. Philadelphia: WB Saunders, 1974.)

- **Function of the placenta:**
  - **1.**The major function of placenta is **diffusion** of <u>food</u> , <u>O2</u> and and <u>excretory products.</u>
    2.in the **Early months of pregnancy,** the placenta membrane is still **<u>thick (it isn't fully developed), surface area is small</u>** (placenta has **<u>not completely grown); therefore the permeability is low & total diffusion conductance is minuscule → oxygenation in this stage is less</u>**
    3.**later** the membrane becomes **<u>thin</u>** and **<u>diffusion area increases</u>** and so the **<u>placental diffusion significantly increases</u>**

- **Major function of placenta:**
  - **Respiration**
  - **Nutrition**
  - **Excretion**
- **Endocrine**
- **Protection**

- Early nutrition → trophoblastic digestion
- Later nutrition → Placenta

Notice that at the beginning, the placental diffusion is low because of (thick membrane, small surface area & the placenta not completely grown) and then gradually it gets higher

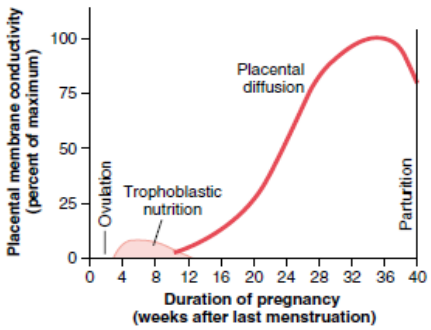
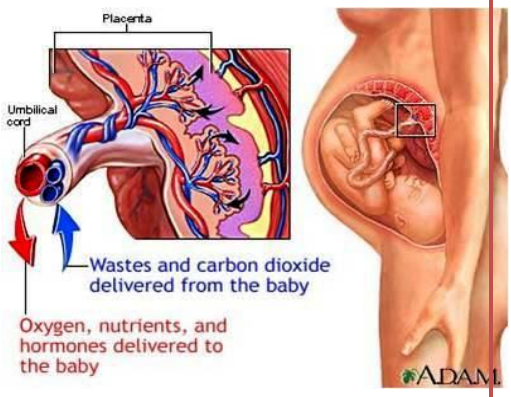


Figure 82-4 Nutrition of the fetus. Most of the early nutrition is due to trophoblastic digestion and absorption of nutrients from the endometrial decidua, and essentially all the later nutrition results from diffusion through the placental membrane.

Respiration:

1. Dissolved O_2 in mother's blood passes to fetal blood by *simple diffusion*



PO_2 50 mm Hg (Maternal) - 30 mm Hg (Fetal) =20 mmHg

* PO2 of the **mother's blood in the placental sinuses** is ~50 mm Hg

* PO2 in the **fetal blood after it becomes oxygenated in the placenta** is ~30 mm Hg

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

- **One might wonder how it is possible for a fetus to obtain sufficient oxygen when the fetal blood leaving the placenta has a PO2 *of only 30 mm H.* There are 3 reasons:**
  1. The hemoglobin of the fetus is mainly *fetal hemoglobin (HbF)* -which is a type of Hb synthesized in the fetus before birth-. **At low PO_2 HbF can carry 20-50% more O_2 than HbA**
  2. **Fetal Hb conc 50% higher than that of the mother (more imp factor)**
  3. **Double Bohr effect**
     i. **low pH in mother's blood (acidic)**
     ii. **High pH in fetal blood (alkaline)**

***Bohr effect=** Hb can carry more oxygen at a low PCO2 (alkaline) than it can at a high PCO2 (acidic); commonly observed in the lungs but also in any other tissue.
*The fetal blood entering the placenta carries **large amounts of CO2**, but much of this CO2 **diffuses** from fetal into maternal blood. Loss of CO2 makes the **fetal blood more alkaline**, whereas the increased CO2 in the **maternal blood makes it more acidic**
→ **capacity of fetal blood to combine with oxygen increases,** and that of **maternal blood decreases**→which forces still more oxygen from the maternal blood while enhancing oxygen uptake by the fetal blood. Therefore, it's called the **Double Bohr effect**; as in it operates in one direction in the maternal blood & the opposite in the foetal blood, making the Bohr effect **twice as important here as it is for oxygen exchange in the lungs**.
^information from the textbook.

2. Diffusion of CO2 Through the Placental Membrane

- CO2 is continually formed in the tissues of the fetus
- **PCO_2 2-3 mm Hg higher in fetal than maternal blood**
- This small gradient is **more than sufficient** to allow adequate diffusion of CO2 because the ***extreme solubility of CO2 in the placental membrane*** allows it to diffuse about **20 times as rapidly as oxygen**
  ***recall: in the adult, the PCO2 gradient for diffusion out of the lung is only about 6 mm Hg (b/w the venous & arterial sides).**

Nutrition

- Fetus uses **mainly glucose** for nutrition so the trophoblast cells in placental villi; which **transport glucose by carrier molecules** (facilitated diffusion)
- **Fatty acids diffuse** due to **high solubility in cell membrane** (more slowly than glucose)
- Ketone bodies, K+, Na+ and Cl- **diffuse** from maternal to fetal blood

Excretion

- Excretory products of the fetus diffuse through placental membrane to maternal blood to be excreted with excretory products of the mother
  - **Urea, uric acid and creatinine**
- **Higher concentration** of excretory products in fetal blood insures **continuous** diffusion of these substances to the maternal blood
  * Excretory products conc. In the fetal blood is always higher than that of the maternal.

Endocrine:

Human Chorionic Gonadotropin (hCG)

- **Glycoprotein**
- **It's most important in the early pregnancy (3-4 month) to maintain corpus luteum & prevent sloughing of the endometrium/menstruation (by ↑estrogen & progesterone) till 13-17 weeks of gestation**
- **Exerts interstitial (Leydig) cell-stimulating effect on testes of the male fetus (growth of male sex organs)**

hCG is **very high** up to the **fifth month of pregnancy** then **it will significantly reduce** BUT estrogen and progesterone then start to increase

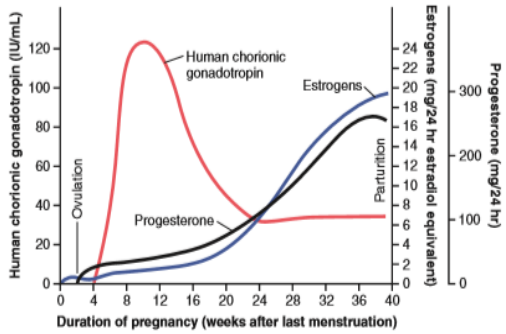


Figure 83-7. Rates of secretion of estrogens and progesterone and concentration of human chorionic gonadotropin at different stages of pregnancy.

Functions of hCG :

- Produced by **syncytiotrophoblasts (8-9 days after fertilization**)
- **Maintains corpus luteum beyond normal lifespan**
- **Stimulates secretion progesterone and estrogen from CL**
- Stimulates **essential DHEA-S in fetal zone of adrenal gland**
- Stimulates **testosterone production in male fetus** (to stimulatd the development of male sexual organs)
- hCG receptors in endometrium and myometrium **can inhibit contractions produced by oxytocin**
- **Immunosuppressant**

Spontaneous abortion will occur if **corpus luteum removed in early pregnancy** (before 7 weeks of pregnancy)

After that the placenta will take over the fxn of progesterone/oestrogen secretion

Under the influence **of hCG**, 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**. If the corpus luteum is removed before approximately the seventh week of pregnancy, **spontaneous abortion almost always occurs**, sometimes even up to the 12th week. After that time, the placenta secretes sufficient quantities of progesterone and estrogens to maintain pregnancy for the remainder of the gestation period. The corpus luteum involutes slowly after the 13th to 17th week of gestation.
From the textbook

- Estrogens (estradiol -mainly-/ estrone / estriol)
  - Steroid hormone
  - Initially produced **by corpus luteum** (first 5-6 wks) - stimulated by **hCG**
  - then placenta (from thw weak androgen DHEA-S from fetal & maternal adrenals)
  - **Increase uterine blood flow**
  - Towards end of pregnancy reaches **30×**
  - Estradiol -- **excreted in urine -- index of fetal well-being**

- Functions in the mother
  - **Enlargement of uterus, breast & external genitalia**
  - **Relaxation of pelvic ligaments in preparation to labor**

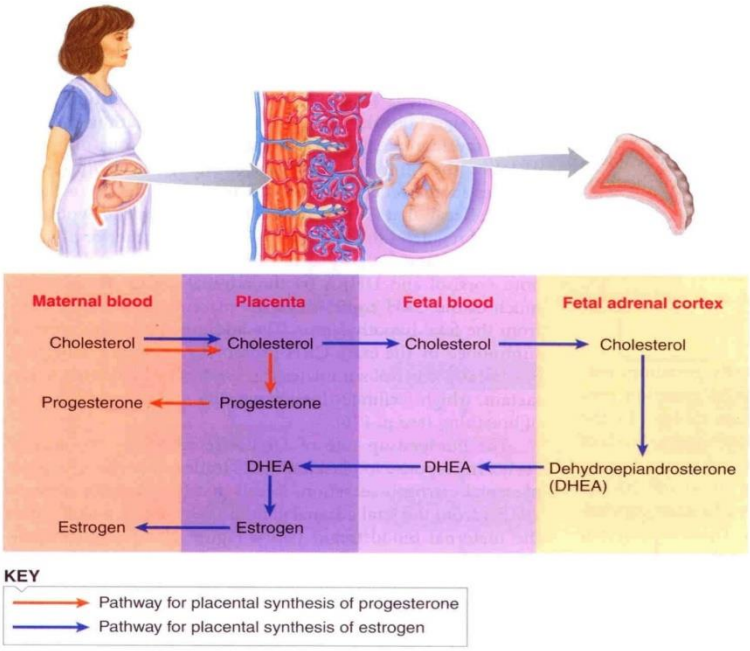


FIGURE 20-31 Secretion of estrogen and progesterone by the placenta. The placenta secretes increasing quantities of progesterone and estrogen into the maternal blood after the first trimester. The placenta itself can convert cholesterol into progesterone *(orange pathway)* but lacks some of the enzymes necessary to convert cholesterol into estrogen. However, the placenta can convert DHEA derived from cholesterol in the fetal adrenal cortex into estrogen when DHEA reaches the placenta by means of the fetal blood *(blue pathway)*.

The doctor mentioned all the pathways in the picture

Progesterone

- **Steroid** hormone
- Secreted by **syncytial trophoblast** cells
- Towards end of pregnancy reaches **10×**
- Derived from **cholesterol**

Remember that progesterone inhibit the contraction of uterus & estrogen stimulates the contraction of it

- Functions in the mother
  - Provides **nutrition** to developing embryo
  - **Development of decidual cells** in the uterine endometrium
  - **Inhibits the contractility of the uterus (therefore allowing for the pregnancy to continue)**
  - Contribute to the **development and cleavage** of the embryo
  - Help estrogen to **prepare mother breast for lactation**

Human Chorionic Somatomammotropin

- **Protein** hormone
- Secreted by placenta around 5th gestational week.
- Secretion ^ in direct proportion to the weight of placenta (ie increased weight of placenta will increase the production)
- It is secreted in **greater** quantities than all other pregnancy hormones together

- Functions in the mother
  - **Breast development** (hPL) (**Human placenta lactogen**)
  - **Similar action to Growth Hormone but weaker**
  - **Inhibits insulin sensitivity =↓ glucose utilization in the mother to make it available to the growth of the fetus.**
  - **Promote release of free fatty acids** from the **fat stores** in the mother to be use by the mother **during pregnancy**
    (so **mother gets her the energy from fat** and **leaves glucose for the fetus**)

Relaxin

- **Polypeptide**
- Secreted by **corpus luteum** and **placenta**

- Functions in the mother **(important in delivery)**
  - **Relaxation of symphysis pubis ligament (weak)**
  - **Softens the cervix at delivery**

Changes in the maternal endocrine system:

1. **Anterior pituitary gland enlargement** (50%)
   - Release of **ACTH, TSH and PRL increase**
   - **FSH and LH almost totally suppressed**
2. **Adrenal gland**
   - **Increase glucocorticoids secretion** (mobilize amino acids)
   - **Increase aldosterone** (retain fluid)
3. **Thyroid gland enlargement (50%)**
   - Increase **thyroxine production (hCG, hCT both secreted by placenta**)
4. **Parathyroid gland enlargement**
   - Increase **PTH secretion** (**maintain normal Ca^{+2}**)

Changes in different organs :

- **Increase in uterine size** (50 gm to 1100 gm)
- The **breasts double in size**
- The **vagina enlarges**
- **Development of edema and acne (**not in all pregnant women **)**
- **Masculine or acromegaly features**
- **Weight gain 10-12 kg** (last 2 trimesters) -baby weight + amniotic fluid/placenta/foetal membranes + extra fluid in the blood & ECF + fat from incr appetite
  - **Increase appetite -** Increased demand for nutrients by fetus & hormonal factor.

Changes in metabolism:

- Increase **basal metabolic rate (15%)**
- Increase in daily requirements for
  - **Iron**
  - **Phosphates**
  - **Calcium**
  - **Vitamins**
    - Vitamin **D (Ca^{+2} absorption**)
    - **Vitamin K** added to **<u>sufficient prothrombin to prevent hemorrhage during birth process</u>**

Changes in circulatory system :

- **Increase in cardiac output** (30-40%) by 27 weeks
- **Increase in blood flow through the placenta**
- **Increase in maternal blood volume** (30%) due to
  - increase **aldosterone and estrogen** (<u>↑ ECF</u>)
  - Increase **activity of the bone marrow** (<u>↑ RBCs</u>)

Changes in respiration:

- **Increase in O_2 consumption (20%)**
  - Increase **BMR**
  - Increase in **body size**
- **Growing uterus presses upwards**
- Increase in **respiratory rate (RR)**
- **Increase in minute ventilation (TV× RR) by 50%**
  - **Progesterone ↑sensitivity of respiratory center (RC) to CO_2**

Maternal kidney function:

1- **Increase renal absorption** for sodium, chloride and water **50%** because increase production of salt and water retaining hormones especially steroid from placenta and adrenal cortex.

2- **Increase glomerular filtration 50%** - as a result of renal vasodilation from Increased NO and relaxin (sheet note : because the volume increased)

Amniotic and its formation :

1-Normal Volume 0.5-1 liter; can increase or decrease
2-Water is replaced once every 3 hours
3-Electrolytes, Na and K are replaced every 15 hours.
4-**Large portion derived from renal excretion by the fetus, small amount by git and lungs**

Preeclampsia and eclampsia: تسمم الحمل - toxaemia of pregnancy

Preeclampsia is rapid rise of BP + proteinuria during *last few months of pregnancy*
The pregnant will develop :
1-Hypertension
2-edema
3- weight gain
4-Decrease RBF & GFR
4-Insufficient blood flow
5-Impair vascular endothelial function
6-Excess water and salt retention
7-some textbooks mentioned that it could be an Autoimmune disease

Eclampsia Extreme degree of preeclampsia (results from untreated preeclampsia)
1- hypertension
2- seizure and coma
3-Greatly decrease kidney output
4-Malfunction of the liver
5-Generalize toxic condition
6-Occurs shortly before birth

That why pregnant women should check their blood pressure at least once a month especially during the last three months