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بسم الله الرحمن الرحيم

Pregnancy & Lactation 2

Final| Lecture 7

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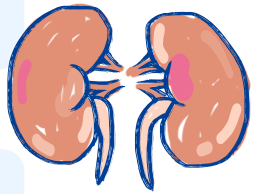


﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾

PREGNANCY & LACTATION II

EBAA M ALZAYADNEH

CHAPTER 83 GUYTON

PHYSIOLOGY DEPARTMENT

ولآخر مرة بنقول:

سموا بالله وما تنسوا الصلاة والدعاء لأهلنا في غزة

الله يجعل اجر هذا العمل في ميزان حسناتنا جميعا والله يوفقكم في اللي جاي :)

Diffusion of Nutrients

- Fetus often uses as much glucose as is used by the entire body of the mother.
- For this the trophoblast cells lining the placental villi provide for *facilitated diffusion* of glucose through its transporters on the placental membrane
- However, the glucose level in fetal blood is 20 to 30 percent lower than that in maternal blood.
- Because of the high solubility of fatty acids in cell membranes, these fatty acids also diffuse from the maternal blood into the fetal blood, but more slowly than glucose, so glucose is used more easily by the fetus for nutrition. This is why the level of glucose is significantly reduced in the fetal blood.
- Also, ketone bodies and potassium, sodium, and chloride ions diffuse with relative ease from the maternal blood into the fetal blood.

Waste Excretion

The placenta is the **only** method by which waste products are filtered from the fetus's blood flow. Thus, a concentration gradient forms for the wastes to diffuse down through.

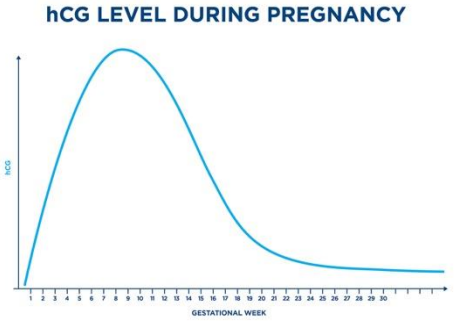
- Excretion from the fetus depends mainly, if not entirely, on the diffusion gradients across the placental membrane and its permeability. Because there are higher concentrations of the excretory products in the fetal blood
- *nonprotein nitrogens* such as *urea, uric acid,* and *creatinine.*
- The level of urea in fetal blood is only slightly greater than that in maternal blood because urea diffuses through the placental membrane with great ease.
- Urea –grad slight----easy
- Creatinine- not easy- greater grad

Urea easily diffuses through the placenta at the chorionic membranes, so no large concentration gradient is present across the membrane. However, **creatinine** does not undergo this easy diffusion, so it does have a notable concentration gradient.

Functions of the Placenta

1. Fetal gut in supplying nutrients
2. Fetal lung in exchanging O2 and CO2
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

Placenta as Endocrine Organ



Human Chorionic Gonadotropin (hCG)- glycoprotein:

- Menstrual sloughing is prevented by the secretion of human chorionic gonadotropin by the newly developing embryonic tissues
- first measured in the blood **8 to 9 days after ovulation** (blastocyst implants). Then reaches the **maximum** concentration at **~10 weeks** of pregnancy and decreases back to low by **16 to 20** weeks till the remainder of the pregnancy.
- Secreted by syncytial trophoblast cells
- Most important function is to maintain corpus luteum (↑estrogen & progesterone) till 13-17 weeks of gestation; the decidual cells must be sustained, as they store glycogen and lipids, which serve as a nutrient source for the blastocyst—greatly swollen and nutritious.
- The endometrial lining secretes uterine milk under the influence of progesterone which is important for the nourishment of the dividing cells. If these functions are lost, spontaneous abortion takes place.
- hCG acts like LH in the sense that it exerts interstitial (Leyding) cell-stimulating effect on testes of the male fetus (growth of male sex organs) by production of testosterone in male fetuses until birth.
    - Without this effect, the dividing fetus will develop with female sex organs.
- Corpus luteum involutes slowly after the 13^{th} to 17^{th} week of gestation.

Maternal-Feto-Placental Steroid Hormone Synthesis

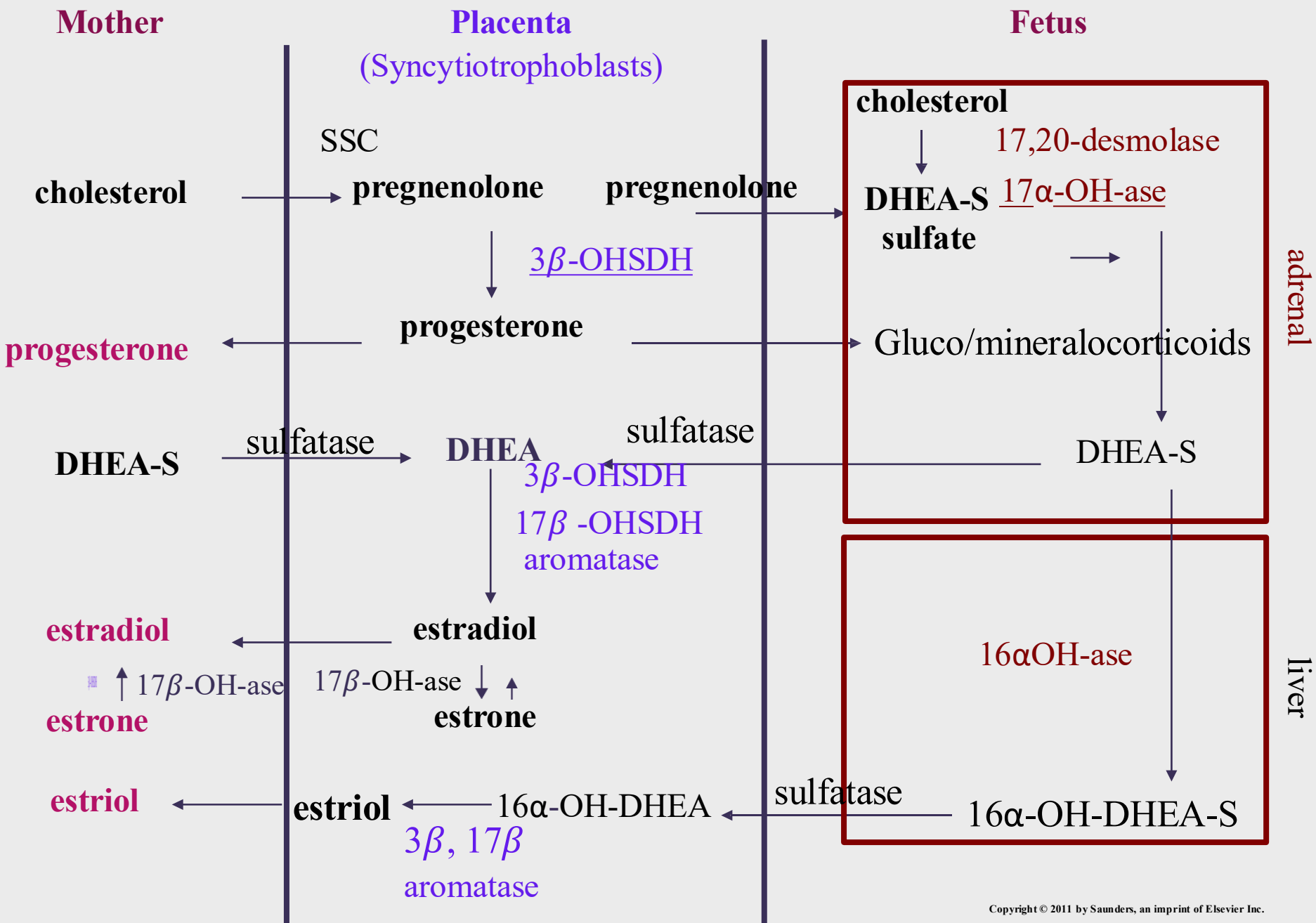


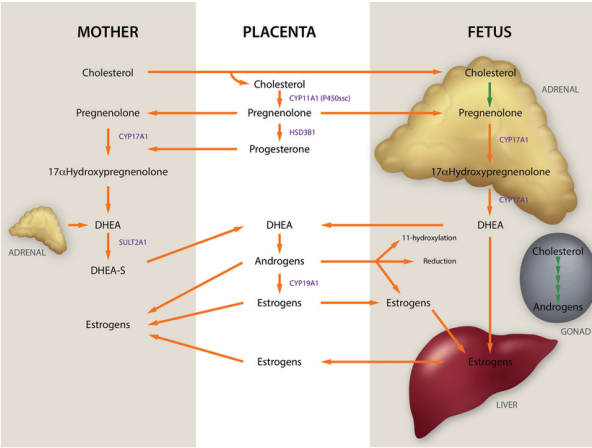
Figure Breakdown

The mother provides cholesterol for the placenta which has the **side chain cleavage enzyme** that converts cholesterol to pregnenolone. The placenta has another enzyme, **3*β*-OHSDH,** that produces progesterone from pregnenolone. The placenta produces progesterone so efficiently that most of the produced amount is secreted back to the maternal circulation to aid in reaching the level of progesterone required for pregnancy.

On the other hand, the placenta is able to produce estrogen but is unable to produce its precursors or convert progesterone to estrogen, for example. Thus, the placenta derives the precursors for estrogen, **DHEA**, from the fetal adrenal gland. The fetal adrenal gland produces DHEA-S (with sulfur), from cholesterol. DHEA-S moves back into the placenta, where the enzymes, **3*β*-OHSDH**, **17*β*-OHSDH**, and **aromatase**, convert it to estradiol. Estradiol is also recirculated back to the mother to help in the continuation of pregnancy.

Estriol requires the fetal liver and adrenal gland for its production. The adrenal gland produces DHEA-S which is then converted in the fetal liver to 16α-OH-DHEA-S by the enzyme 16α-hydroxylase. Then, 16α-OH-DHEA is formed by sulfatase in the placenta, which is then converted to estriol.

Estriol acts as a marker for the fetus's wellbeing and the communication between the different fetal organs (liver and adrenal gland).



Maternal & Fetoplacental Steroidogenesis

1) Progesterone pathway (the placenta is strong):

Step A: Mother supplies cholesterol, enters placenta.

Step B: Placenta converts cholesterol → pregnenolone

Enzyme in placenta: **SCC** (side-chain cleavage enzyme = CYP11A1)

Step C: Placenta converts pregnenolone → progesterone

Enzyme: **3β-HSD** (3β-hydroxysteroid dehydrogenase)

Step D: Progesterone goes back to the mother (and supports pregnancy)

Progesterone is crucial for: maintaining endometrium/decidua, reducing uterine contractions, supporting pregnancy continuation

Maternal & Fetoplacental Steroidogenesis

2) Estrogen Pathway (placenta needs fetal help)

The placenta makes the pregnancy estrogens (**estradiol, estrone, estriol**)

BUT: The placenta lacks **CYP17** (17α-hydroxylase / 17,20-desmolase). The placenta cannot efficiently make DHEA (the androgen precursor) from pregnenolone/progesterone. So, it depends on the fetal adrenal to make DHEA-S.

3) Fetal Adrenal ("precursor factory")

Fetal adrenal: Cholesterol → DHEA-S route

Uses enzymes: 17α-OH-ase (CYP17) and 17,20-desmolase (also part of CYP17 activity).

Production of DHEA-S (dehydroepiandrosterone sulfate) water-soluble which makes it able to diffuse into the placenta from the maternal circulation.

Fetal adrenal makes: glucocorticoids/mineralocorticoids from progesterone.

Maternal & Fetoplacental Steroidogenesis

4) Placenta converts fetal DHEA-S into estrogens

DHEA-S reaches the placenta:

Step A: DHEA-S → DHEA

Removes sulfate by **sulfatase**

Step B: Placenta uses: **3β-HSD, 17β-HSD → toward estrogens**

aromatase (CYP19) (very important)

DHEA → androstenedione/testosterone → aromatase → estrone/estradiol

Estrone (E1) and **Estradiol (E2)** come largely from this pathway

Key takeaway:
Placenta is excellent at **aromatization** (turning androgens → estrogens). But placenta needs fetal adrenal **DHEA-S** input first.

Maternal & Fetoplacental Steroidogenesis

5) Estriol (E3): the special one that needs fetal liver

Step A: Fetal liver adds 16α-OH group

Enzyme : **16α-OH-ase**

Converts: **DHEA-S → 16α-OH-DHEA-S**

Step B: Back to placenta for final conversion

In placenta: **sulfatase** removes sulfate then **aromatase** + **other enzymes** convert it into **estriol (E3)**

Estriol (E3) is a marker of **fetal + placental cooperation**, because it requires fetal adrenal (DHEA-S), fetal liver (16α-hydroxylation), and placenta (sulfatase + aromatase).

Maternal & Fetoplacental Steroidogenesis

- Pregnancy steroids come from teamwork:
  - Mother supplies **cholesterol**
  - **P**lacenta makes **p**rogesterone
  - Fetal **adrenal** supplies **DHEA-S**
  - **Placenta** converts DHEA-S to **estradiol/estrone**
  - Fetal **liver** modifies DHEA-S to make **estriol**

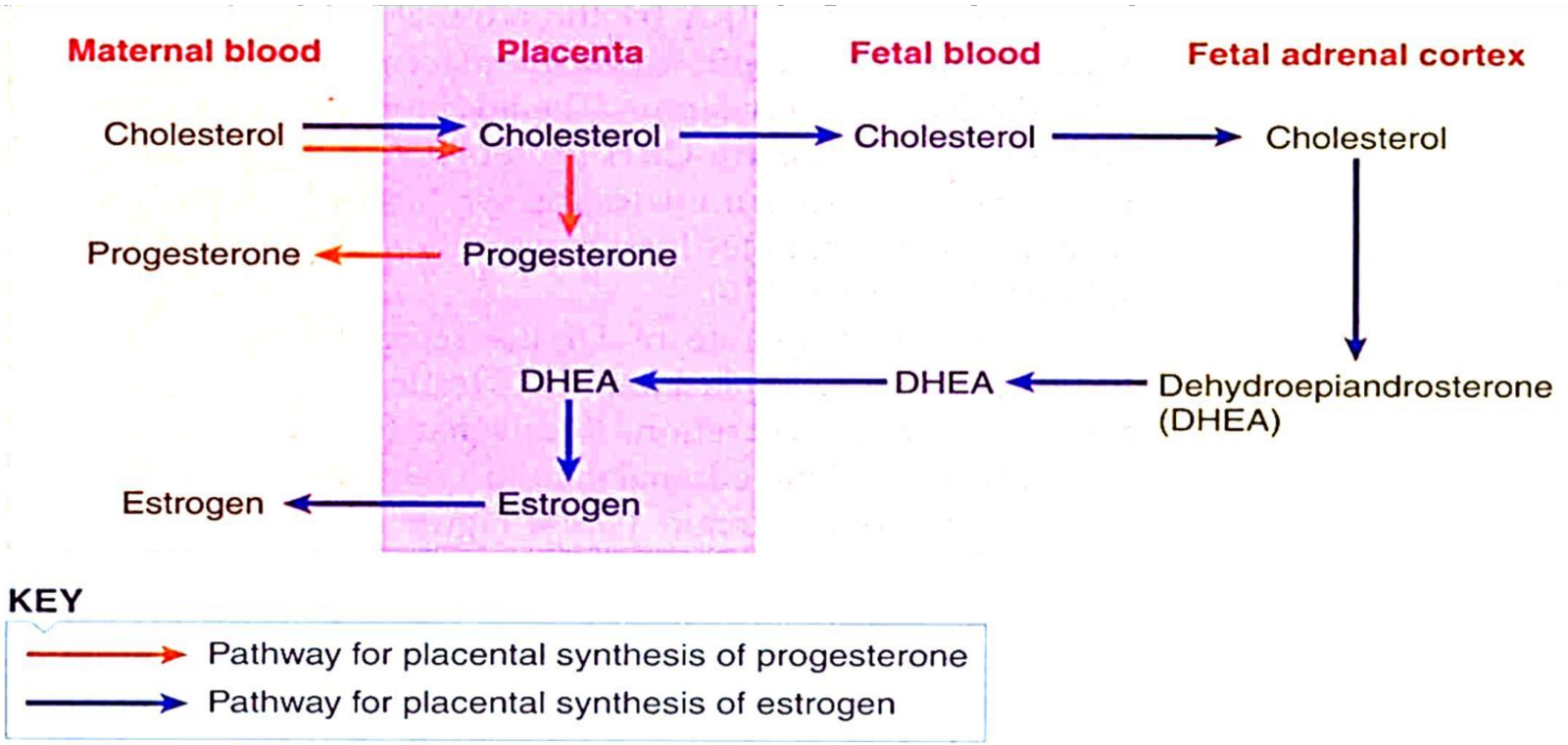


FIGURE 20-31 Secretion of estrogen and progesterone by the placenta. The placenta secretes increasing quantities of progesterone and estrogen into the maternal blood after the first trimester. The placenta itself can convert cholesterol into progesterone *(orange pathway)* but lacks some of the enzymes 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)*.

Placenta as Endocrine Organ

PROGESTERONE

Progesterone is essential for a successful pregnancy; moderate quantities by the corpus luteum at the beginning of pregnancy, then later in large quantities by the placenta (10x) by syncytial trophoblast cells from cholesterol.

Effects of progesterone in pregnancy:

1. Progesterone causes decidual cells to develop in the uterine endometrium (nutrition of the early embryo)
2. Progesterone decreases the contractility of the pregnant uterus, thus preventing spontaneous abortion.
3. Progesterone contributes to the development of the conceptus (dividing cells) before implantation (secretions of the mother's fallopian tubes and uterus to provide nutrition for the developing morula and blastocyst).
4. Believed that progesterone affects cell cleavage in the early developing embryo.
5. Helps estrogen prepare the mother's breasts for lactation.

Progesterone-Produced by Placenta

1. Most important for establishment and sustenance of morula and blastocyst.

2. Maintains decidual lining of uterus to provide nutrition for fetus.

3. Produced by placenta formed from cholesterol (90% goes to mother); is major substrate for cortisol and aldosterone by fetal adrenal gland.

4. Inhibits uterine contractions-- inhibits prostaglandin production and decreases sensitivity to oxytocin.

Changes in Maternal Endocrine System

Due to maternal metabolic load and response to placenta hormones:

- **Anterior pituitary gland** enlargement (50%)
  - Release of ACTH, TSH and PL (corticotropin, thyrotropin, and prolactin)
  - FSH and LH almost totally suppressed (?) this is due to the high concentrations of estrogen and progesterone.
- **Adrenal gland**
  - Increase glucocorticoids secretion (mobilize amino acids).
  - Increase aldosterone (2x) (retain fluid) pregnancy-induced hypertension.
- **Thyroid gland enlargement** (50%) thyroxine production
  - thyrotropic effect of hcG and TSH, and placenta human chorionic thyrotropin
- **Parathyroid gland** enlargement
  - Increase PTH secretion (maintain normal Ca^{+2}) to ossify bones of fetus

Placenta as Endocrine Organ

ESTROGEN

- Secreted by syncytial trophoblast cells of placenta
- Towards the end of pregnancy, it reaches 30x its original level.
- Derived from **weak androgen (DHEA)** released from **maternal** & **fetal adrenal cortices.**
- 30 times the mother's normal level

Functions in the mother

- Enlargement of uterus, breast (and ductal) & external genitalia
- Relaxation of pelvic ligaments in preparation for labor (sacroiliac joints, symphysis pubis)
- Activation of the uterus (gap junctions); this is thought to make the smooth muscle contractions more efficient.
- In the 3rd trimester, [estrogen] > [progesterone], this is believed to contribute to the contractility of uterine muscles in preparation for labor.

Estradiol

- Estradiol is the most important estrogen. It is Initially produced by corpus luteum (first 5-6 wks) stimulated by hCG, then placenta (from DHEA-S from fetus)

- Increases uterine blood flow, which is especially important for the growth of the fetus and placenta.

- **Estriol** → excreted in urine → index of fetal well-being

Pregnancy Hormones

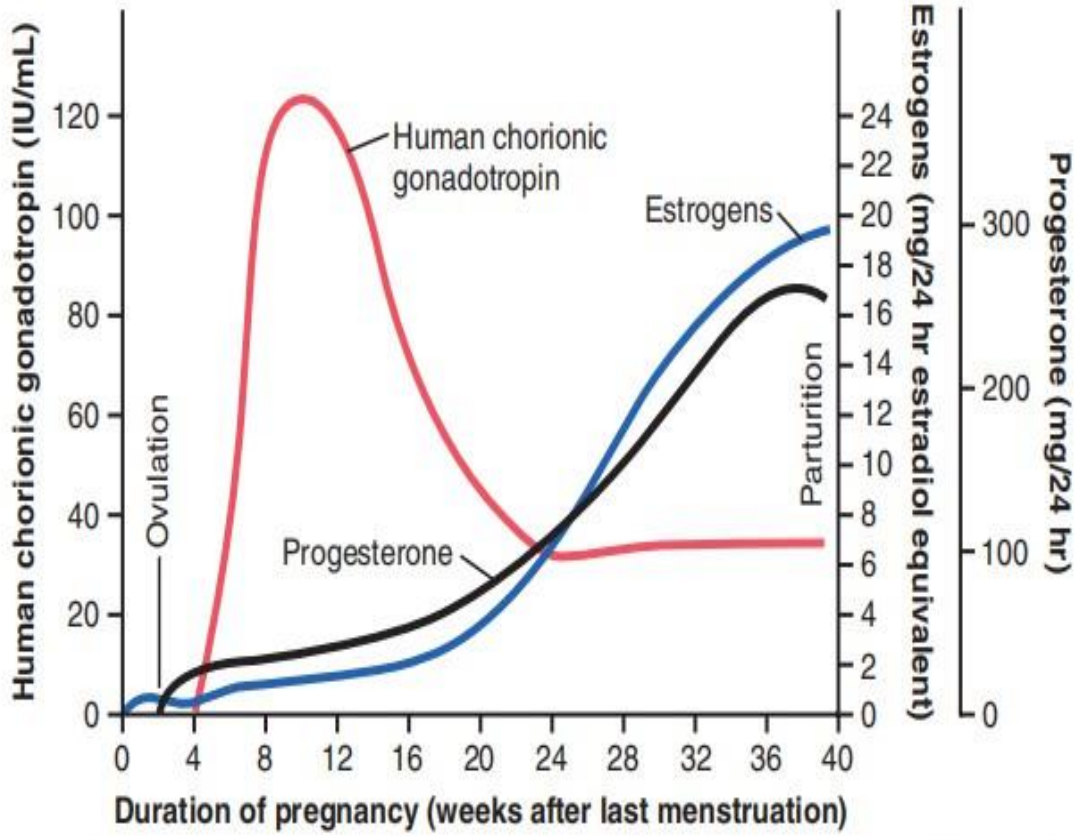


Figure 83-7. Rates of secretion of estrogens and progesterone and concentration of human chorionic gonadotropin at different stages of pregnancy.

Discussed in the previous lecture

Placenta as Endocrine Organ

- Human Chorionic Somatomamotropin or Human placental lactogen (hPL)
  - Protein hormone
  - Secreted by placenta around 5th gestational week
  - quantities several times greater than that of all the other pregnancy hormones combined

- Functions in the mother (not all well known)
  - Breast development (cant induce milk in human)
  - Weak growth hormone's action(100x less)
  - Inhibits insulin sensitivity =↓glucose utilization by mother. hPL decreases insulin sensitivity to spare more glucose for the fetus, allowing glucose to remain in the maternal circulation longer for transport to the fetus.
  - Promotes release of fatty acids (source of energy)
  - Mainly metabolic actions

Placenta as Endocrine Organ

- Relaxin
  - Polypeptide
  - Secreted by corpus luteum and placenta

- Functions in the mother
  - Relaxation of symphysis pubic ligament (weak effect)
  - Softens the cervix at delivery
  - vasodilator (may increase blood flow, venous return and cardiac output)

Morning sickness

- **Occurrence** → 70% of pregnancies
- **Onset** → 4-8 wks gestation (early pregnancy); improvement before 14-16 wks
- **Mechanisms**: (NOT well understood)
  - Relaxation of smooth muscle of stomach
  - ? Increase hCG → serum levels don't correlate well
- Higher frequency of female fetus → 56% Usually (not that much increase)
- Associated with more favorable outcome

Changes in different organs

- Increase in uterine size (50 gm to 1100 gm)
- The breasts double in size
- The vagina enlarges
- Development of edema because of water retention and acne due to androgens.
- Masculine or acromegalic features
- Weight gain 10-12 kg (last 2 trimesters)(~4kg fetus)
  - Increase appetite
  - Removal of nutrients by fetus
  - Hormonal effect

Metabolism

- There are very significant metabolic changes during pregnancy, all of which are important for fetal growth.
- Increase basal metabolic rate (15%) due to thyroxine ACTH sex hormones
- Increase in daily requirements for
  - Iron
  - Phosphates
  - Calcium
  - Vitamins - vitamin D (Ca^{+2} absorption)

Kidney function during pregnancy

- The renal tubules' reabsorption capacity for sodium, chloride, and water is increased as much as 50%
  - Cortical and placenta steroid hormones which have effects similar to mineralocorticoids.
  - The renal blood flow and GFR increase up to 50%
  - Tubuloglomerular feed back
  - NO or relaxin which increase renal blood flow.
- Normal pregnant woman accumulates only about ~2.5 kg of extra water and salt.

  Excreted after delivery

Kidney function during pregnancy

- Kidney function increases: GFR by 40%, RPF by 75%
- Increase Na and H2O reabsorption by tubule → E2
- Insulin secretion increases after 3rd mo of pregnancy. Insulin secretion increases because insulin sensitivity decreases. Through feedback mechanisms, insulin release continues to be stimulated because tissues are less responsive to insulin. At the same time, insulin still promotes growth and anabolism.
- Maternal response to insulin decreased
- NO change to glucagon

Kidney function during pregnancy

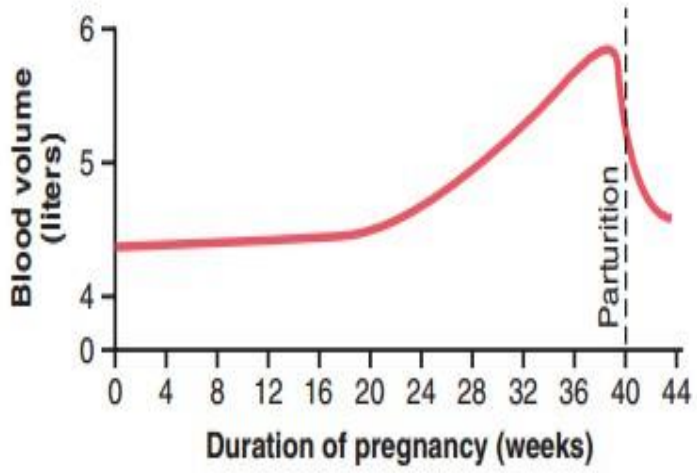
- Early: Plasma Na decreased despite Na retention; also decreased osmolarity
- by 10 wks, thirst and AVP not suppressed until reach new threshold → new "osmostat"
- AVP levels same as prepregnant due to inc vasopressinase (1000x by term) made by the placenta
- During early pregnancy, vasopressin (ADH) helps the body retain more water. This is important because the mother needs a larger blood volume to supply the uterus, placenta, and growing fetus.
- Even though water retention increases, the level of vasopressin in the blood does not rise much because the placenta produces an enzyme called **vasopressinase**, which breaks down the hormone. So, the effect of vasopressin is still maintained, especially during the first 10 weeks of pregnancy, so the body continues to retain water.
- Later in pregnancy, the mother's body adapts by resetting the osmolarity "set point." This means the body accepts a slightly lower plasma osmolality and sodium concentration during pregnancy.

Kidney function during pregnancy

- Increased aldosterone, renin, angiotensinogen due to E2 → may be stimulated by reduction in effective circulating bld vol caused by large placental blood pool
- BP increases slightly: 86.4 (11-12 wks); 90.3 (36-38) decreases close to term
- TPR decreased because of vasodilation.
- Increased Ca reabsorption, increased 25- OH-vit D, 1,25-(OH)2-vit D
  Activated vitamin D increases calcium absorption to provide calcium for the fetus.

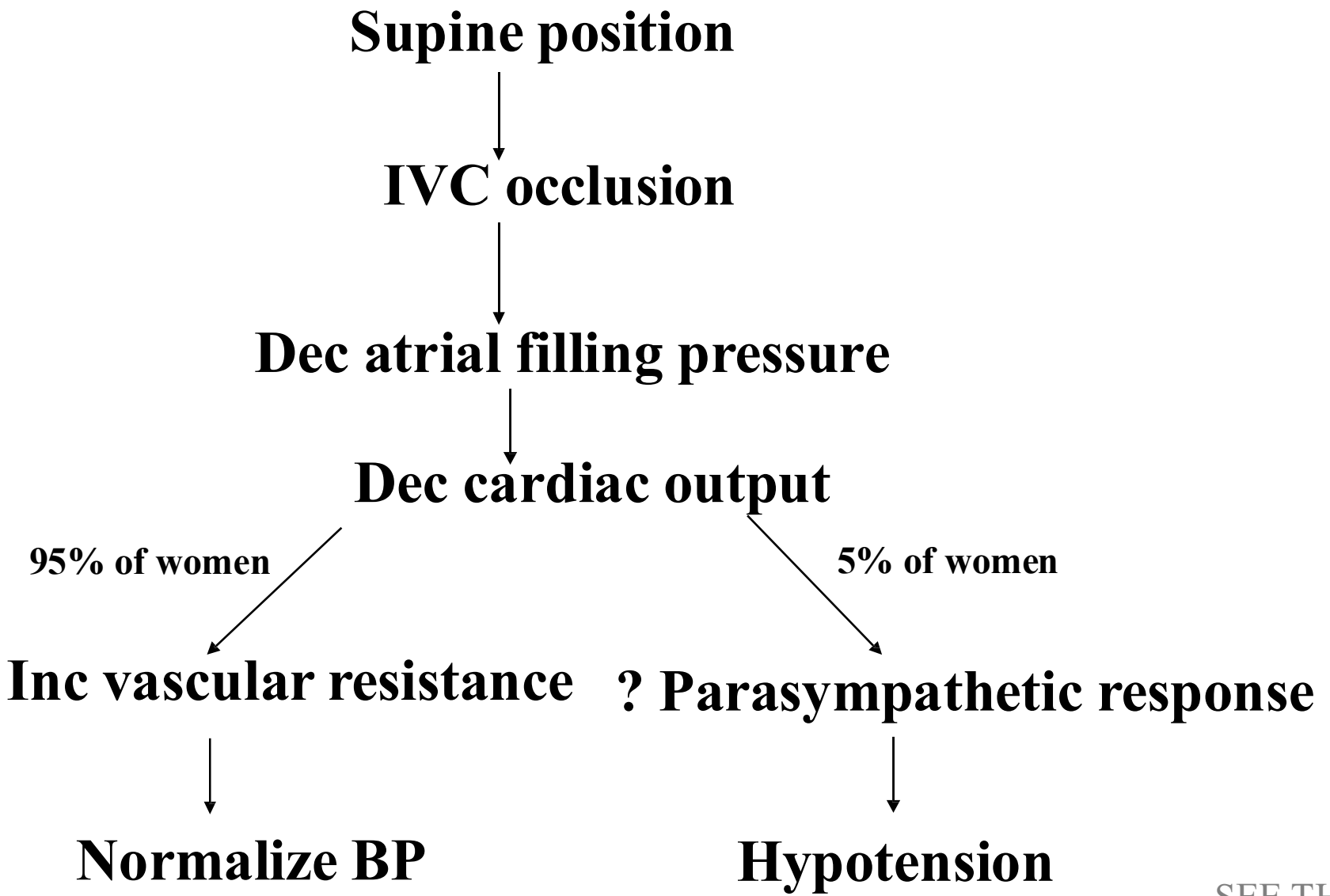
Changes in circulatory system

- Increase in blood flow through the placenta, 625 ml/min
- Increase in maternal blood volume (30%) due to
  - Increase aldosterone and estrogen (↑ECF)
  - Increase activity of the bone marrow (↑RBCs)
  - (1-2 L extra-safety factor)



- Blood Flow and Cardiac Output Increase During Pregnancy (30-40%) by 27th weeks.
- As metabolic activity increases, local circulation and arteriolar vasodilation increase, leading to greater blood flow and venous return.
- Due to increased metabolism and blood flow
- The cardiac output falls in the last 8 weeks of pregnancy
  - blood flow in some other tissue(s) may be reduced.

Supine hypotension syndrome in pregnancy



SEE THE NEXT SLIDE

Supine hypotension syndrome in pregnancy

- One symptom that may occur in pregnant women, especially during the last trimester, is supine hypotension syndrome. Because of the growing fetus, its weight, and surrounding fluids, the inferior vena cava (IVC) gets compressed in supine position.

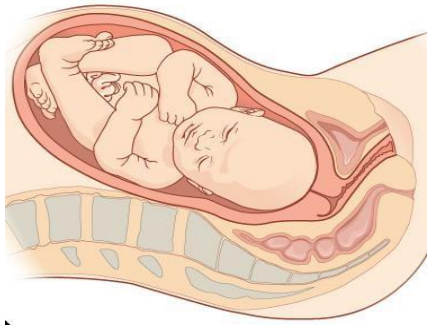
- This reduces venous return, atrial filling pressure, and cardiac output. When the woman stands, the baroreflex normally compensates.

- In about 95% of women, vascular resistance increases and blood pressure normalizes. However, in about 5% of women, a paradoxical parasympathetic response may occur, resulting in hypotension.

Changes in respiration

- Increase in O_2 consumption (20%)
  - Increase Basal Metabolic Rate
  - Increase in body size
- Increase in respiratory rate (RR)
  - Progesterone ↑ sensitivity of respiratory center to CO_2. (Even a small increase in CO_2 can produce much stimulation to the respiratory center).
  - the growing uterus presses upward against the abdomin, whichpress upward against the diaphragm, so the total excursion of the diaphragm is decreased. Thus respiratory rate is increased to maintain the extra ventilation
- Increase in minute ventilation by 50% and a decrease in arterial PCO_2 to several ml
- increased tidal volume (40%) → causes dec in maternal plasma CO2 → slight alkalosis

Amniotic fluid



- Normally, the volume of amniotic fluid 500ml -1L
- The water in amniotic fluid is replaced once every 3 hours and the electrolytes sodium and potassium are replaced an average of once every 15 hours.
- A large portion of the fluid is derived from renal
  - excretion by the fetus.
- Some absorption occurs by way of the gastrointestinal tract and lungs of the fetus.
- Amniotic membranes contribute to exchange of amniotic fluid through diffusion, fluid formation and absorption into the placenta.
- 2 functions:

1. Mechanical buffer → protects fetus
2. Mechanism by which fetus excretes waste → turns over daily, renal excretions (75%), pulmonary secretion

Mechanisms starting “labor”

“Fetal genotype controls length of gestation (parturition)” 3 theories:

1. Removal of progesterone; change in estrogen: progesterone ratio (high estrogen-to-progesterone ratio, or a lower progesterone-to-estrogen ratio)
2. Increase in uterotonins: oxytocin
3. Prostaglandins are also major contributors (PGF 2α and PGE2)

“Positive feedback” theory of parturition

- Stretch of cervix by fetus’s head elicits reflex increase in contractility of uterus pushing the baby forward which in turn further stretches the cervix setting up positive feedback loop.

- Weak contractions stretch the cervix, where sensory receptors transmit stretch signals to the hypothalamus, creating a positive feedback loop that induces stronger contractions. These contractions initially begin weakly and may start during the last three months before labor.

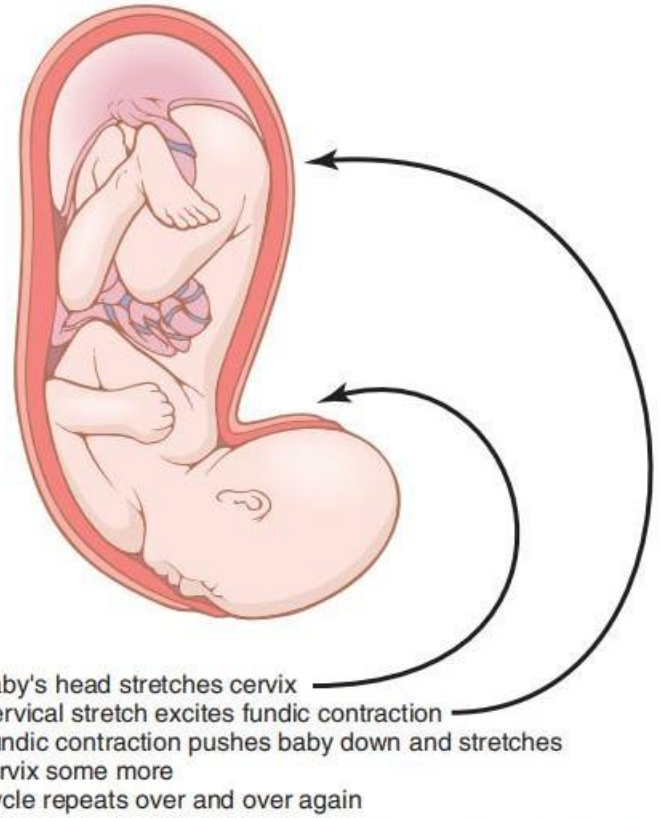


Figure 83-9. Theory for the onset of intensely strong contractions during labor.

Labor:

- Braxton-Hicks contractions → irritability of uterine muscle → weak, slow contractions → begins about 1 mo before labor
- In contrast: stronger contractions stretch cervix and force baby through birth canal

- True labor has circadian rhythym, peaks between 12 midnite and 5 am.

- "labor pains" → due to ischemia of uterine muscle in early stage, then stretch of cervix, perineum, vagina

Induction of labor

- **Prostaglandins**
- Oxytocin -- Pitocin
- Prostaglandins play a role in labor induction even if labor has not yet started, regardless of whether membrane rupture has occurred. Synthetic prostaglandins or synthetic oxytocin (Pitocin) may be used to induce labor or augment weak labor contractions.

- Induction--stimulate spontaneous onset of labor with or without ruptured membranes

- Augment-- stimulate contractions following spontaneous rupture of membranes -- stimulate spontaneous contractions that are inadequate because of failure of progressive dilatation and descent

- Oxytocin most important in Phase 3: Women may receive extra oxytocin following placental delivery to prevent bleeding

Lactation

- Breast development: begins at puberty due to estrogen stimulation then Progesterone continues alveolar and lobular development of the breast.
- increases during pregnancy, due to estrogen, progesterone and
- prolactin: promotes milk secretion
  - secreted by anterior pituitary, starting from 5th wk of pregnancy until birth, then cycles
  - Milk letdown is initiated after delivery, and oxytocin plays an important role in this process. Oxytocin is released with each nursing episode to promote milk ejection. It also has beneficial effects on the uterus, helping it return to its normal size and reducing uterine bleeding, which is why breastfeeding is encouraged after delivery.

- 1st milk = colostrum -- same proteins and lactose as milk, but no fat

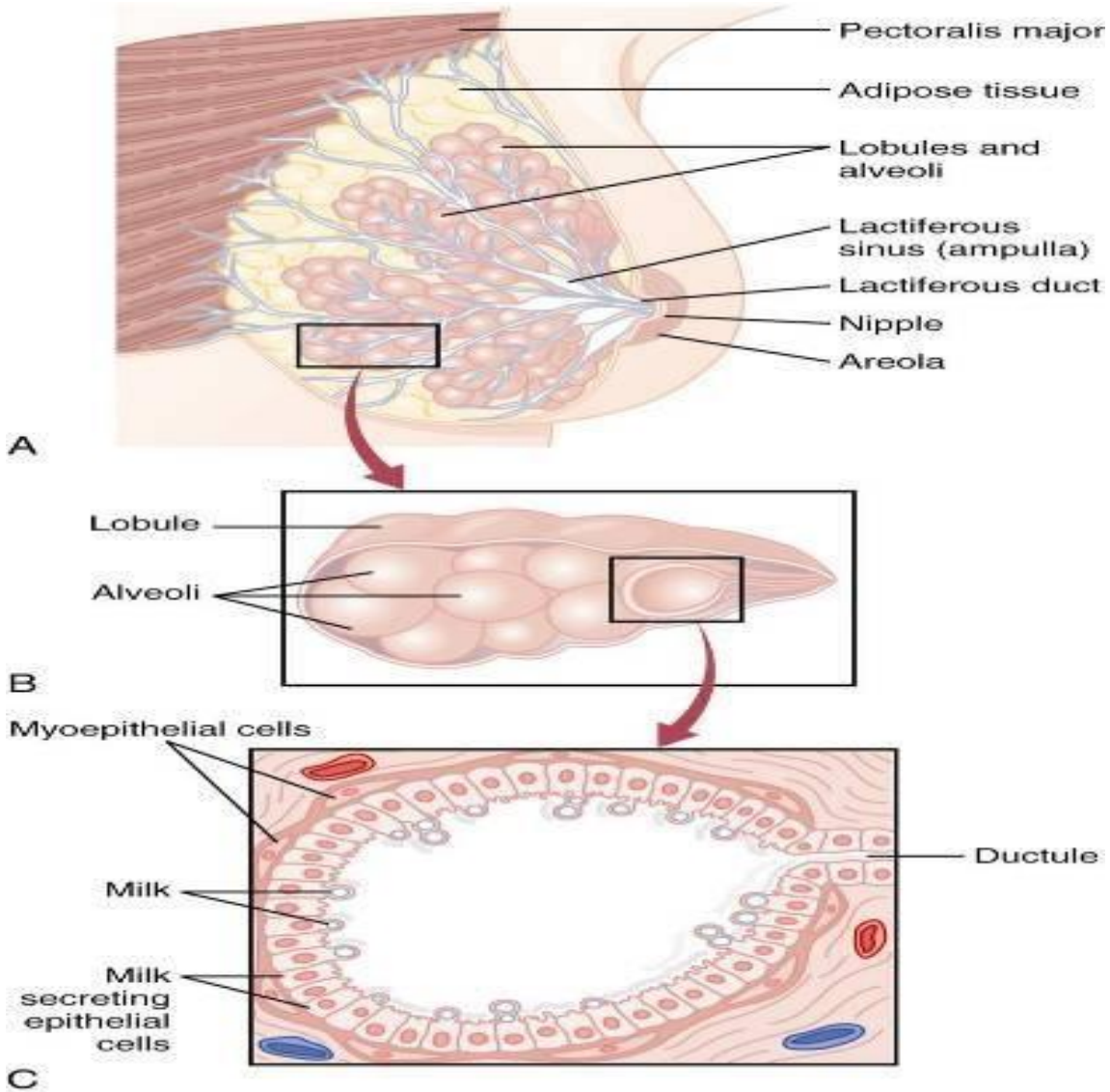
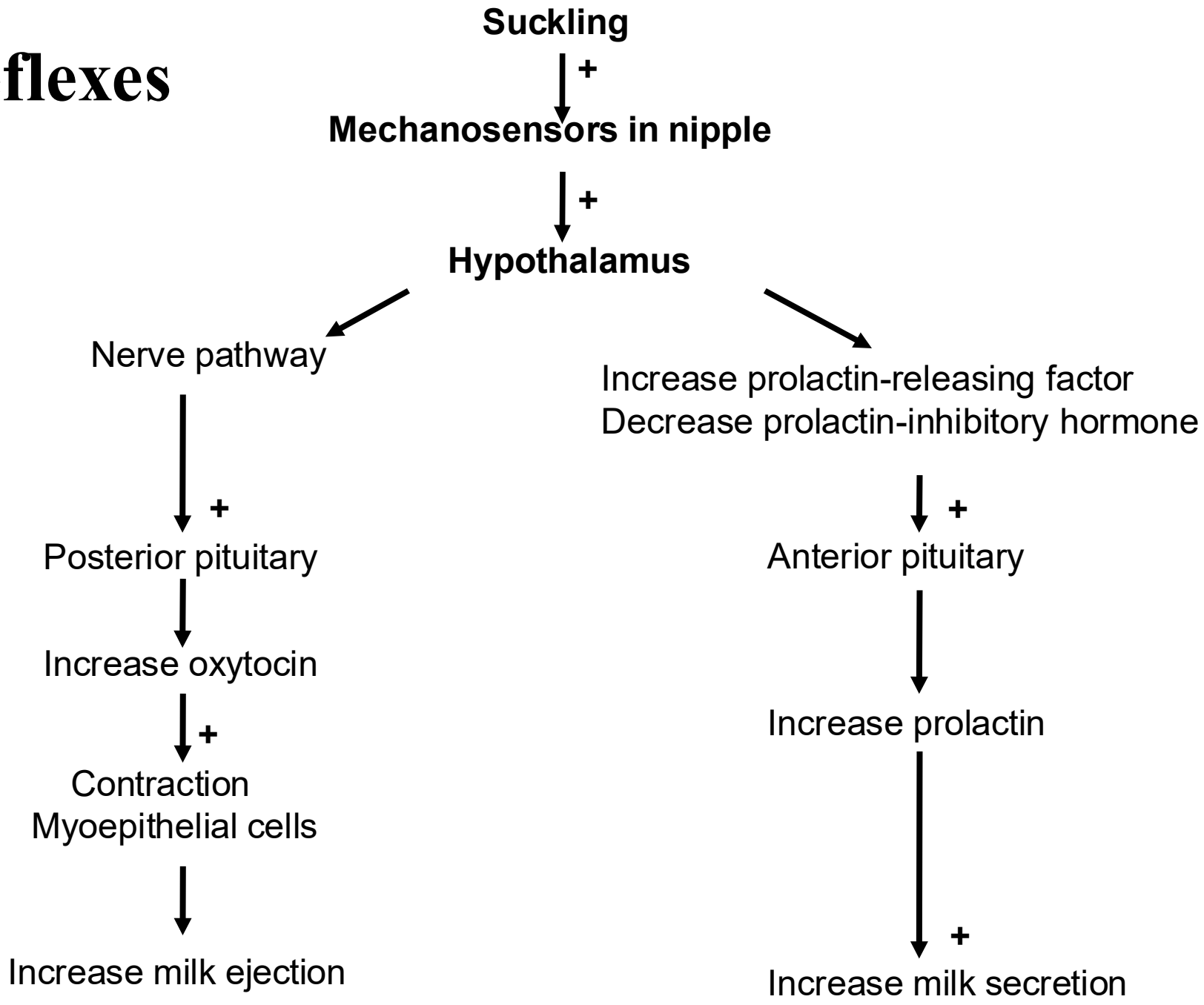


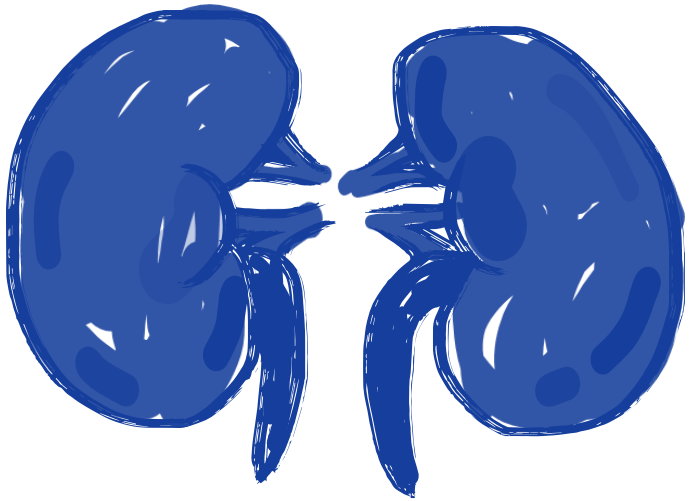
Figure 82-10 The mammary gland.

Suckling reflexes



Lactation

- Initiated by precipitous drop in estrogen and progesterone after delivery
- prolactin surges each time mother nurses baby due to nerve impulses from nipples to hypothalamus → without nursing stimulation, no prolactin surge, and loss of milk production
- A prolactin surge occurs with every episode of suckling and becomes programmed in the brain according to nursing times. Therefore, if the mother delays nursing, she may already feel breast engorgement because prolactin secretion has been programmed to surge at that time.
- When not nursing, hypothalamus produces prolactin inhibitory hormone
- Lactation inhibits FSH, LH and thus lactation interferes with reproductive function
- During lactation, regular menstrual cycles are usually absent because prolactin suppresses FSH, and LH secretion. Later, the body may adapt and FSH may initiate a new cycle, but in most cases it remains suppressed (As breastfeeding decreases, ovarian cycles may gradually resume).



PHYSIOLOGY QUIZ LECTURE 7

رسالة من الفريق العلمي

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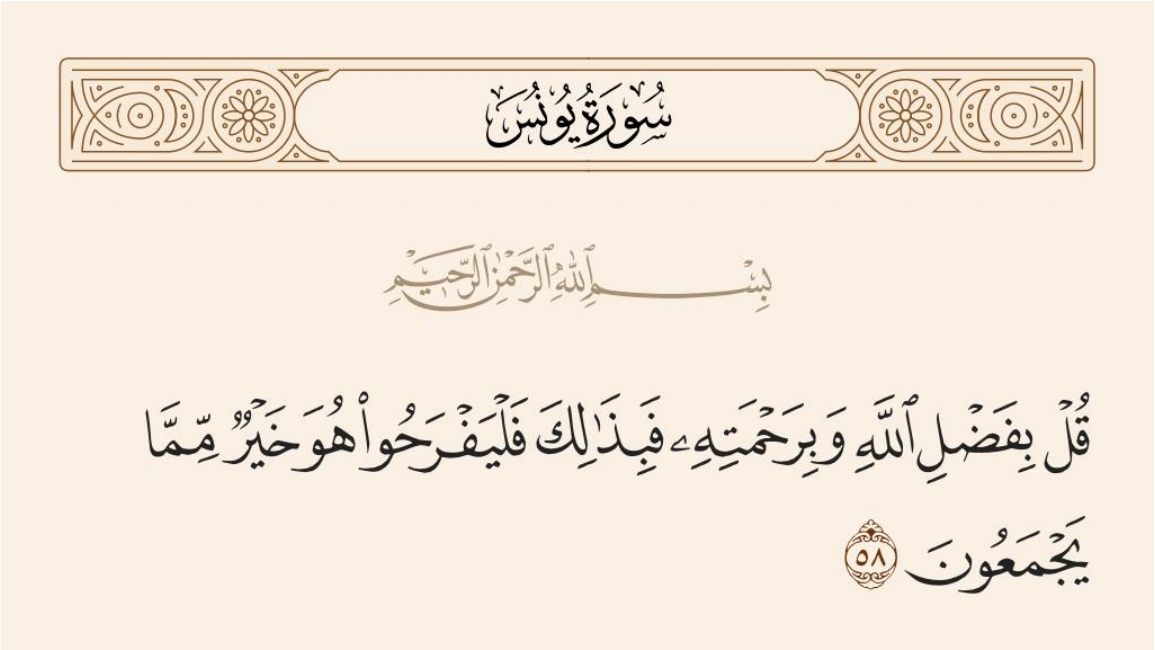

سبحانك اللهم وبحمدك نشهد أن لا إله إلا أنت نستغفرك ونتوب إليك
لا تنسوا زميلنا عمر عطية وزميلتنا روضة ضياء من دعائكم
ولا تنسونا من صالح دعواتكم ، بالتوفيق

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Corrections from previous versions:

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