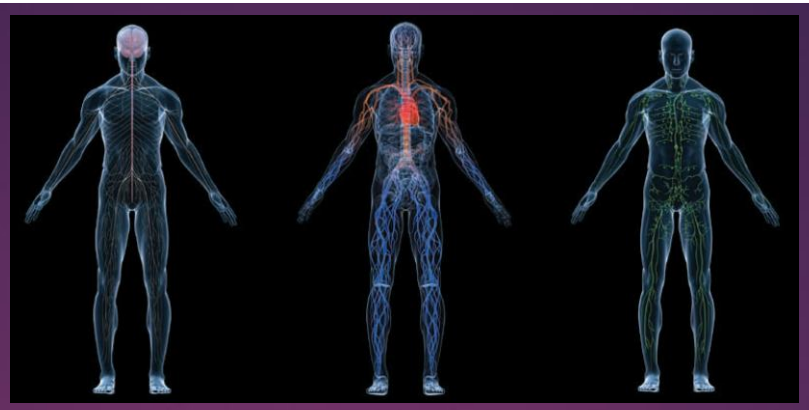
Chapter 82:



PREGNANCY AND LACTATION

EBAA M ALZAYADNEH

CHAPTER 83 GUYTON

PHYSIOLOGY DEPARTMENT

Lecture II

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 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.

- Also, ketone bodies and potassium, sodium, and chloride ions diffuse with relative ease from the maternal blood into the fetal blood.

Wastes excretion

- 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 gard

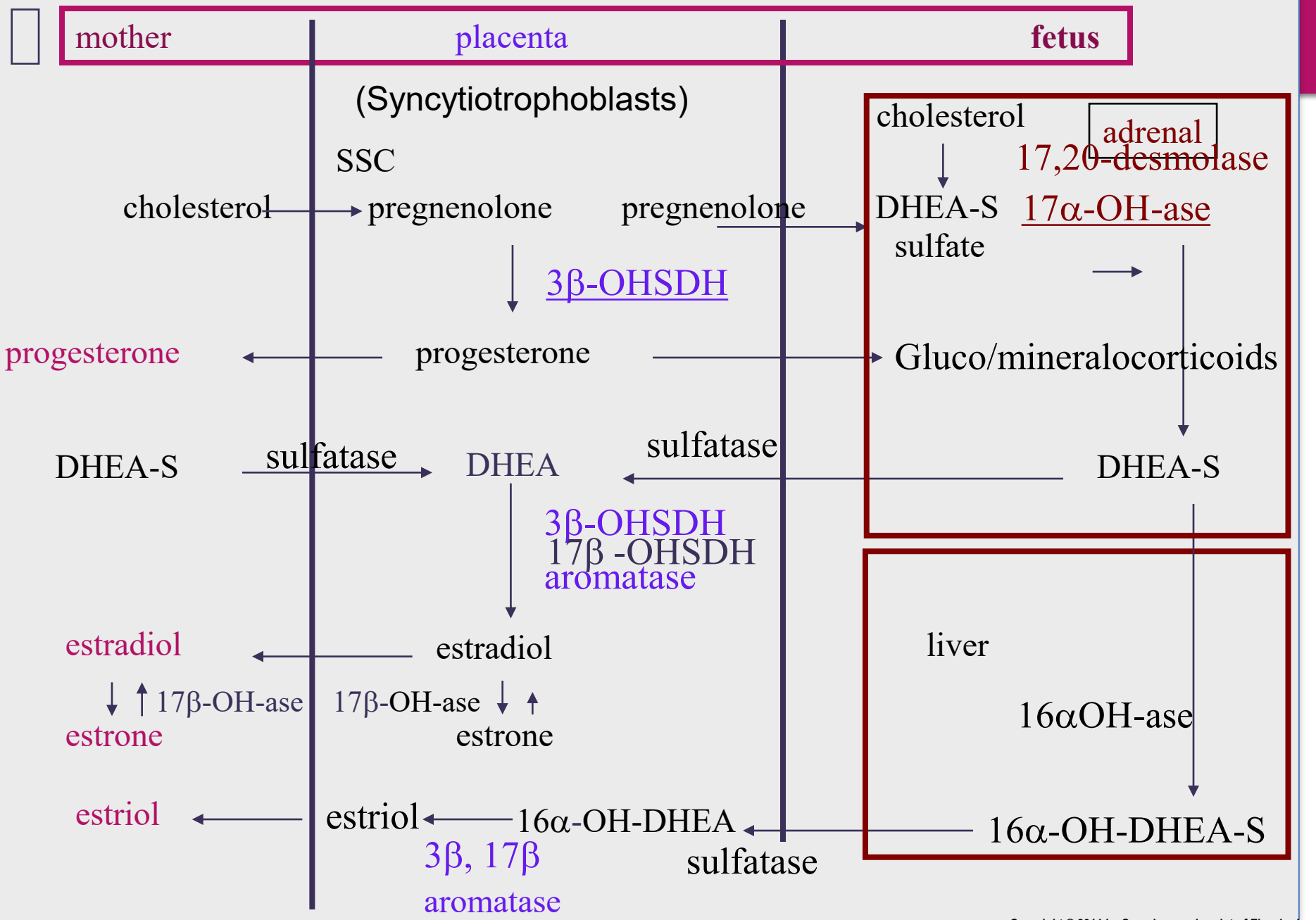
Functions of the placenta

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 max 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; decidual cells—greatly swollen and nutritious
- 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.
- corpus luteum involutes slowly after the 13th to 17th week of gestation.

Maternal-feto-placental steroid hormone synthesis



Maternal and 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**) **Cholesterol → pregnenolone**
- **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 and fetoplacental steroidogenesis

2) Estrogen pathway (placenta needs fetal help)

- The placenta makes the pregnancy estrogens (**estradiol, estrone, estriol**) BUT:
- ❌ The placenta **lacks CYP17** (17a-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 (the "precursor factory")**
- **fetal adrenal**: **Cholesterol → DHEA-S route**
- Uses enzymes: 17a-OH-ase (CYP17) and 17,20-desmolase (also part of CYP17 activity)
- production of **DHEA-S (dehydroepiandrosterone sulfate)** water-soluble
- fetal adrenal makes:
- **glucocorticoids/mineralocorticoids** from progestrone

Maternal and fetoplacental steroidogenesis

4) Placenta converts fetal DHEA-S into estrogens

- **DHEA-S** reaches the placenta:
- **Step A: Removes sulfate by** : **sulfatase**
  DHEA-S → DHEA
- **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 and 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)
- placenta (sulfatase + aromatase)

Maternal and fetoplacental steroidogenesis

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

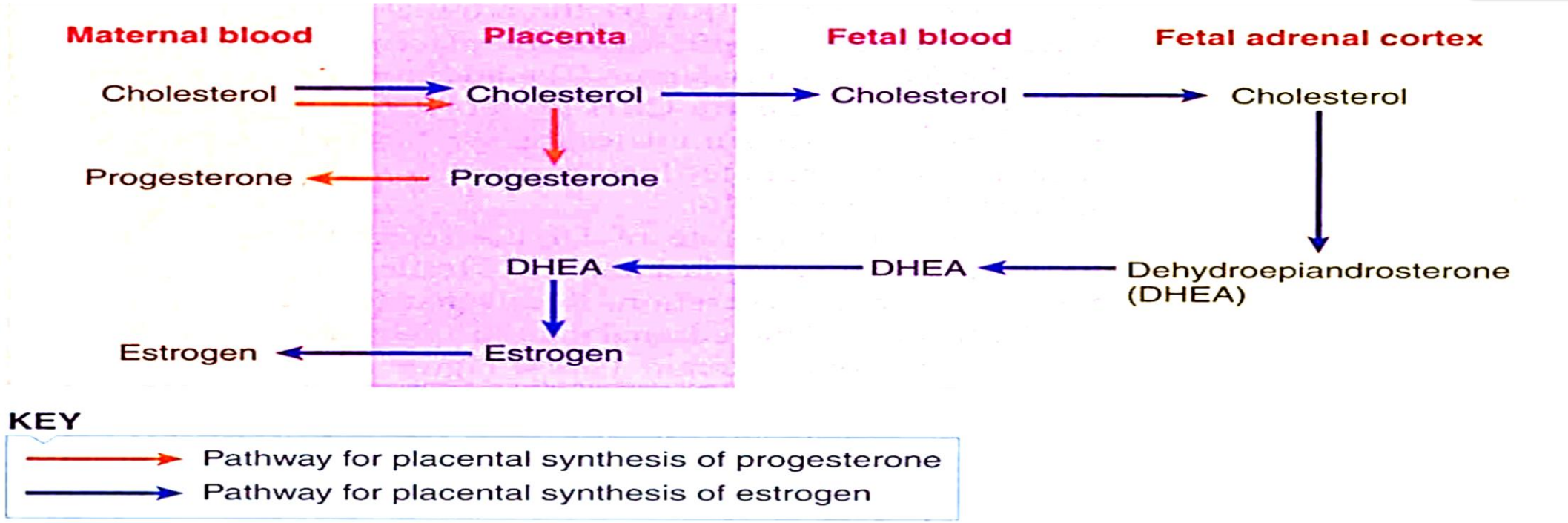


FIGURE 20-31 Secretion of estrogen and progesterone by the placenta. The placenta secretes increasing quantities of progesterone and estrogen into the maternal blood after the first trimester. The placenta itself can convert cholesterol into progesterone *(orange pathway)* but lacks some of the enzymes 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
- 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 before implantation(secretions of the mother's fallopian tubes and uterus to provide nutritition 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 (?)
- Adrenal gland
  - Increase glucocorticoids secretion (mobilize aminoacids)
  - 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 30×
  - Derived from weak androgen (DHEA) released from maternal & fetal adrenals cortex
  - 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)

Estradiol

-- initially produced by corpus luteum (first 5-6 wks) stimulated by hCG

--then placenta (from DHEA-S from fetus)

inc. uterine blood flow

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

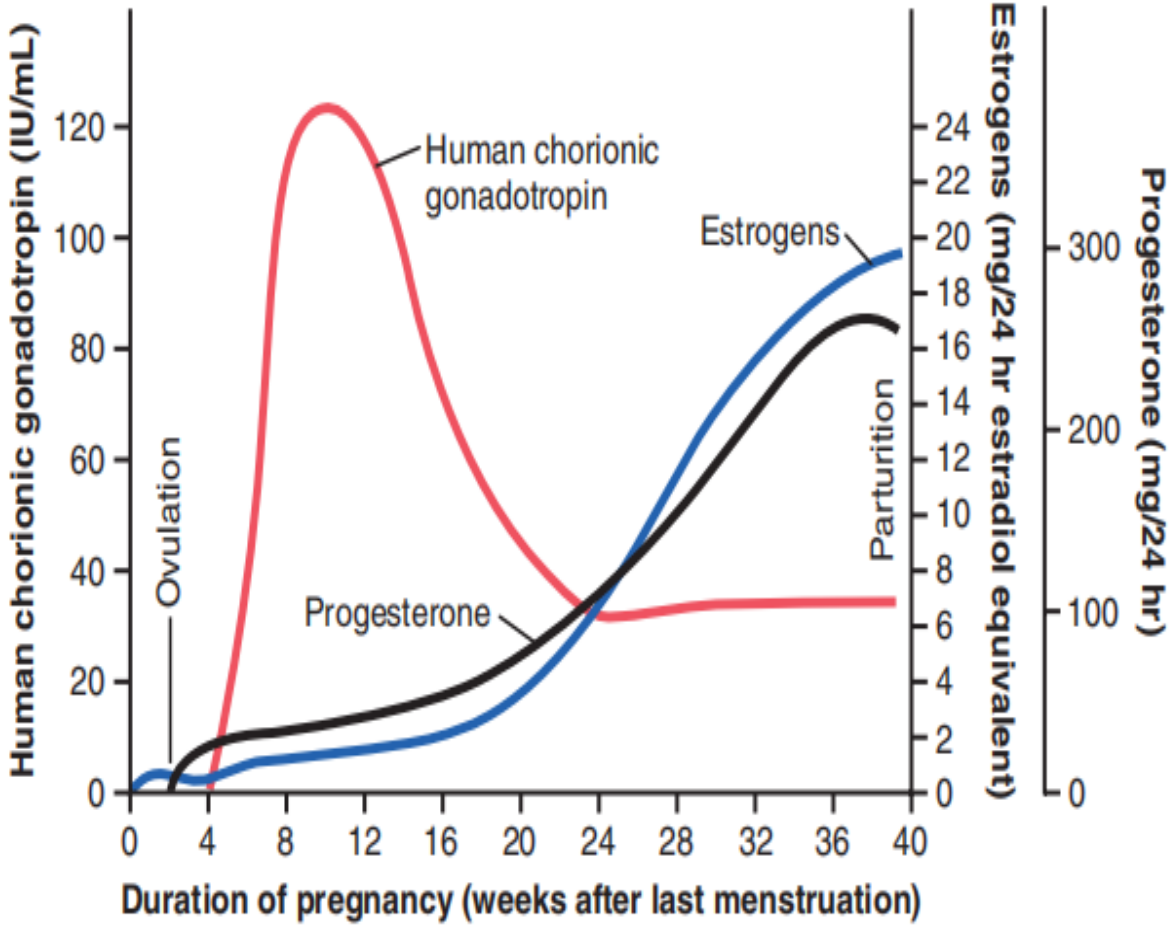


Figure 83-7. Rates of secretion of estrogens and progesterone and concentration of human chorionic gonadotropin at different stages of pregnancy.

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
  - 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; improvement before 14-16 wks

Mechanisms:

- Relaxation of smooth muscle of stomach
- ? Inc hCG -- serum levels don't correlate well

Higher frequency of female fetus -- 56%

Usually 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 and acne
- Masculine or acromegalic features
- Weight gain 10-12 kg (last 2 trimesters)(~4kg fetus)
  - Increase appetite
    - Removal of nutrients by fetus
    - Hormonal effect

Metabolism

- 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
  - The renal blood flow and GFR increase up to 50%
  - Tubuloglomerular feed back
  - NO or relaxin
- Normal pregnant woman accumulates only about ~2.5 kg of extra water and salt. Excreted after delivery

Kidney function increases: GFR by 40%, RPF by 75%

Incr. Na and H2O reabsorption by tubule--E2

Insulin secretion increases after 3rd mo of pregnancy

Maternal response to insulin decreased/no change to glucagon

Early: Plasma Na decreased despite Na retention; also dec 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

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

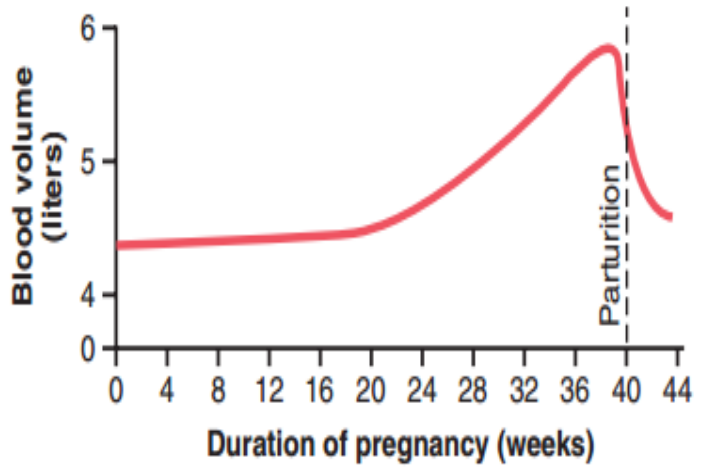
Increased Ca reabsorption, increased 25-OH-vit D, 1,25-(OH)2-vit D

Changes in circulatory system

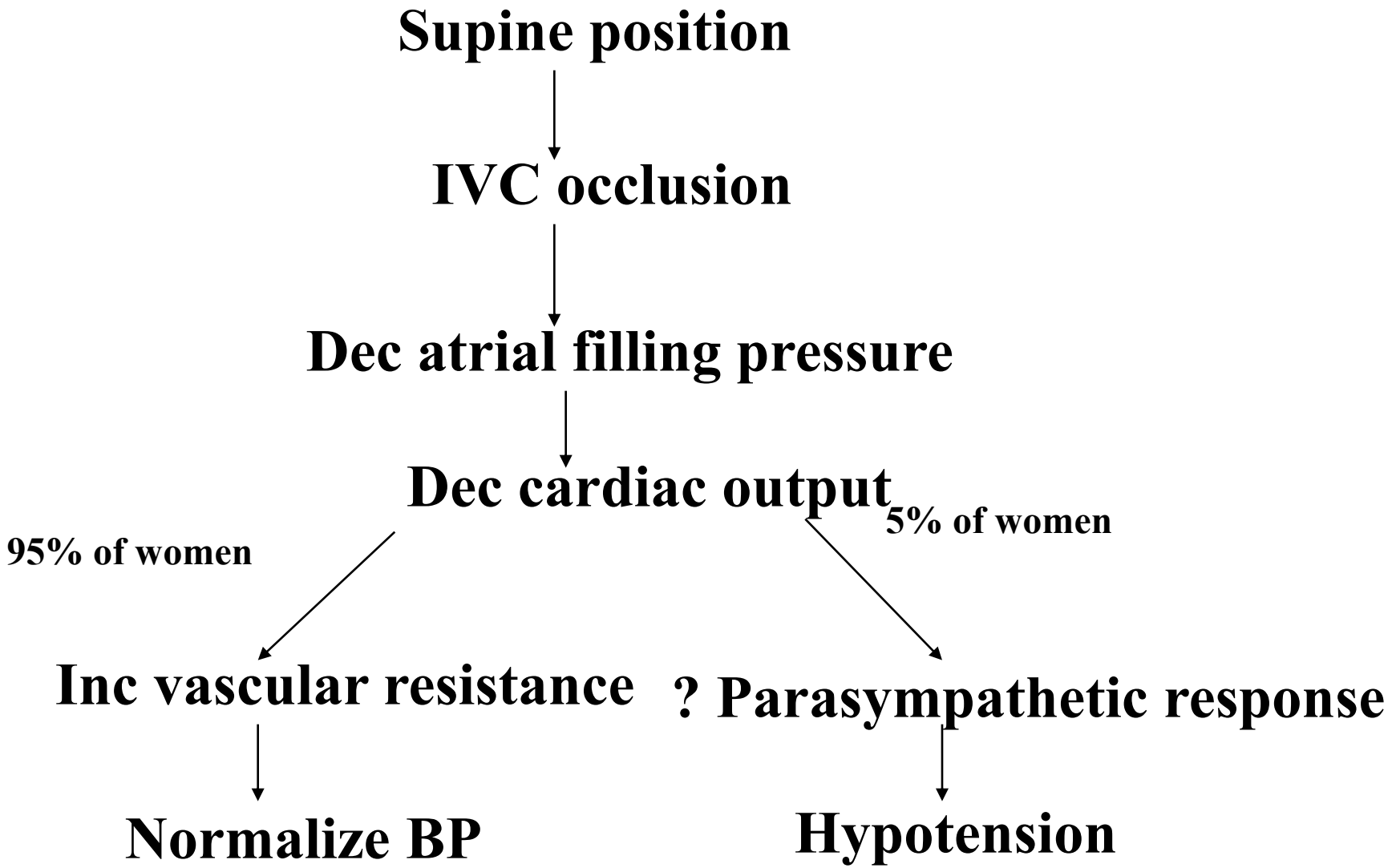
- Increase in blood flow through the placenta, 625 ml/min
- Increase in maternal blood volume (30%) due to
  - Increase aldosterone and estrogen (↑ ECF)
  - Increase activity of the bone marrow (↑ RBCs)
  - (1-2 L extra-safety factor)
- Blood Flow and Cardiac Output Increase

During Pregnancy (30-40%) by 27th weeks.

- Due to increased metabolism and blood flow
- the cardiac output falls in the last 8 weeks of pregnancy, blood flow in
  - blood flow in some other tissue(s) may be reduced.



Supine hypotension syndrome in pregnancy

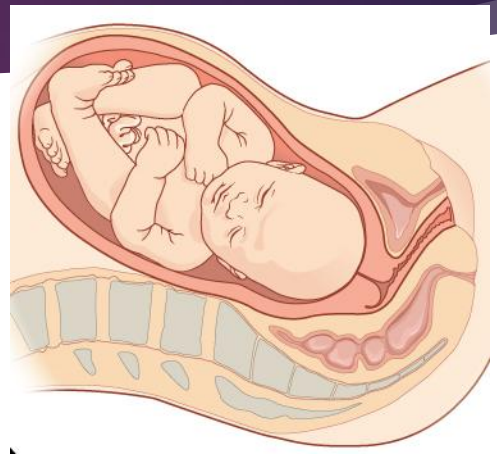


Changes in respiration

- 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
  - the growing uterus presses upward against the abdomin, which press 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 formation and absorption

Amniotic fluid

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”

3 theories:

1. Removal of progesterone; change in estrogen: progesterone ratio

2. Increase in uterotonins: oxytocin

3. 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.

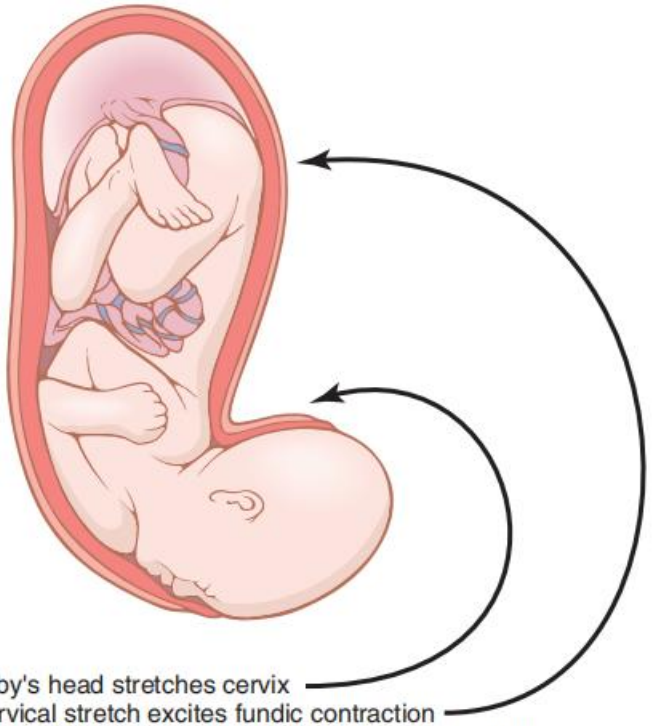


Figure 83-9. Theory for the onset of intensely strong contractions during labor.

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™

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

--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

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

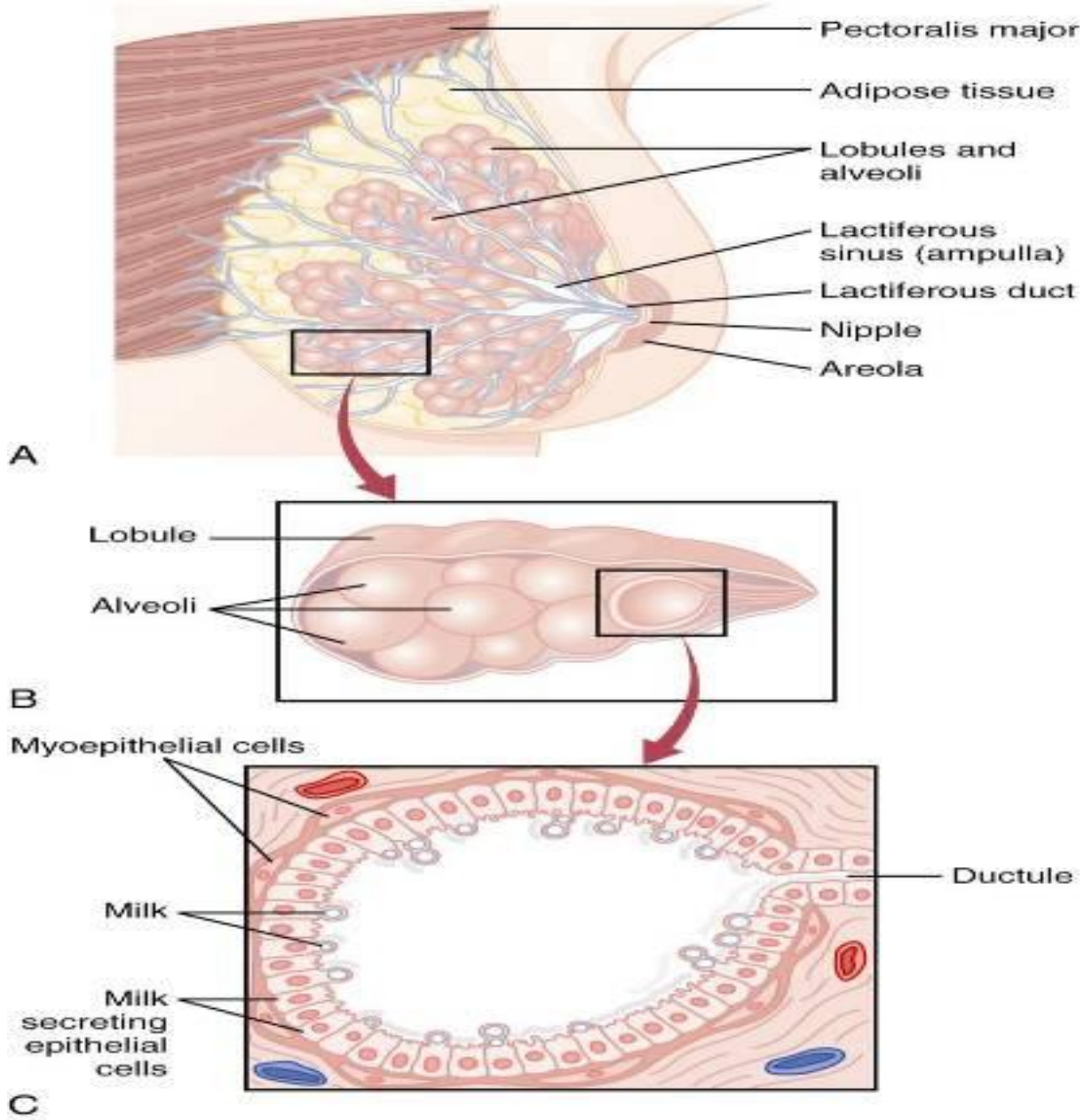
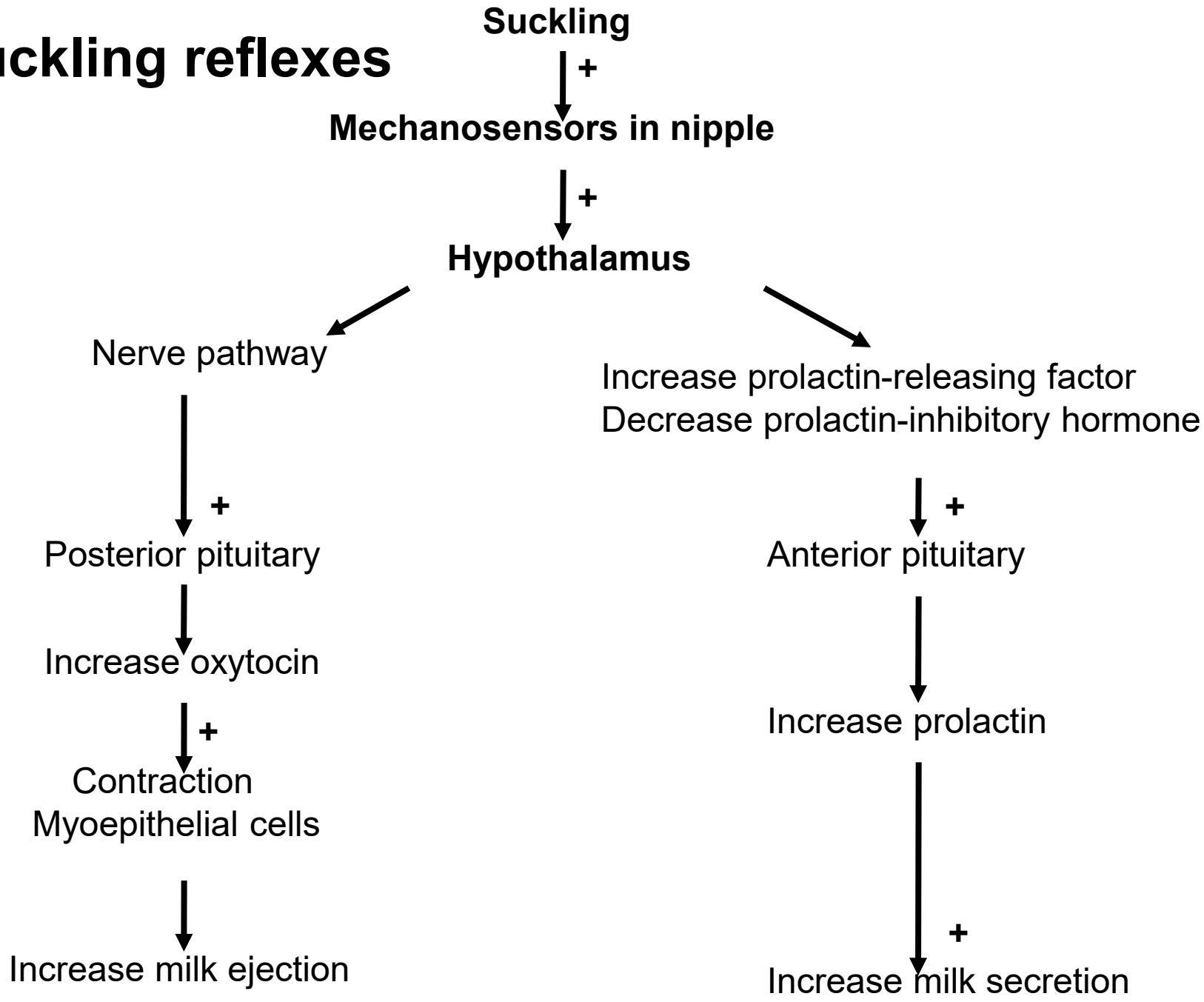


Figure 82-10
The mammary gland.

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

When not nursing, hypothalamus produces prolactin inhibitory hormone
Lactation inhibits FSH, LH and thus lactation interferes with reproductive function