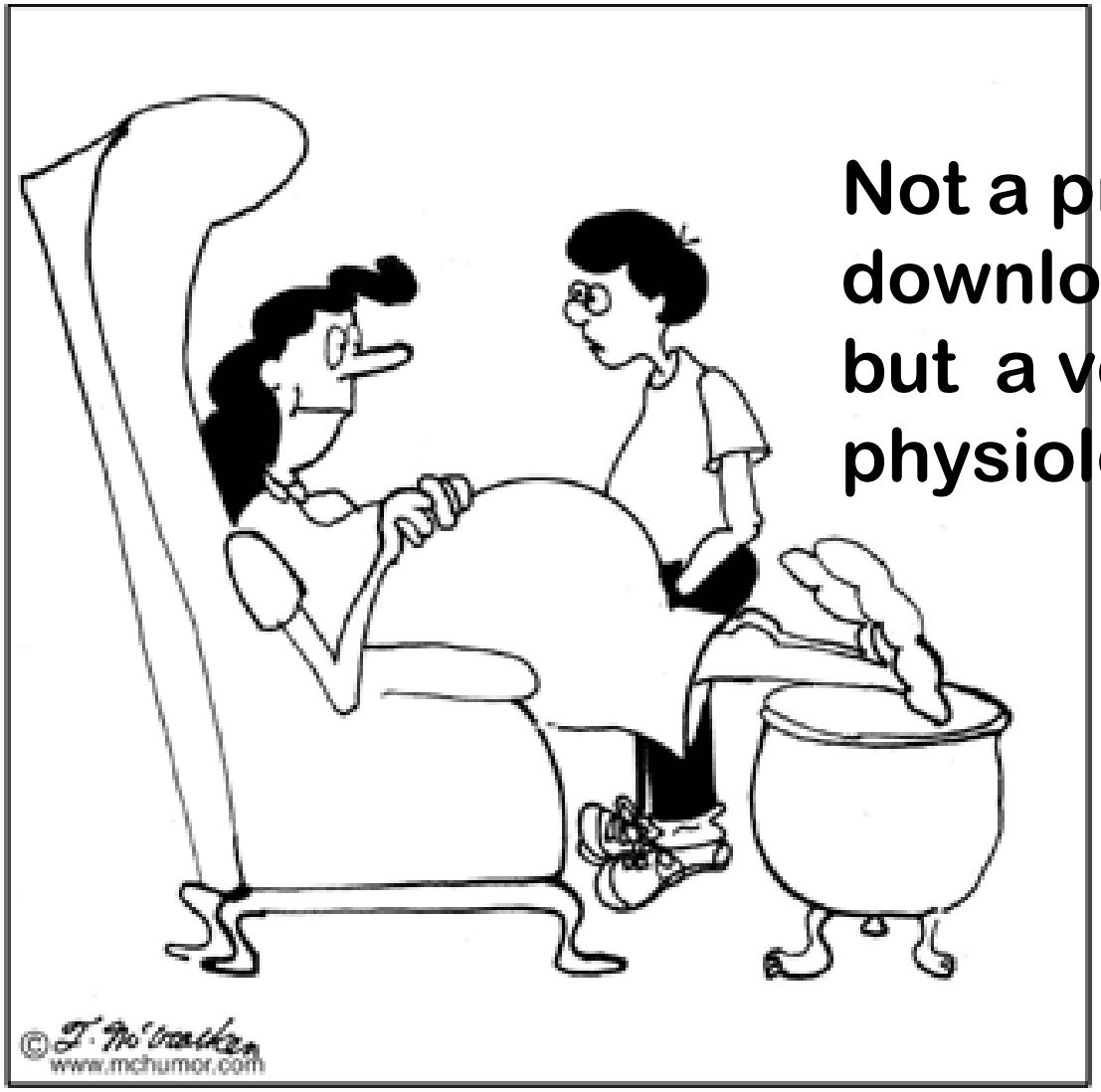
Physiology of Pregnancy



"Mom, when will you be finished downloading the new baby?"

Not a process of simply downloading from the Net, but a very complicated physiological activity

Fertilization & Implantation

Fertilization & Implantation

- **Fertilization** occurs in **ampulla** of uterine tube.

(1) **chemoattraction** of the sperm to the ovum by substances produced by the ovum

(2) **adherence** to the **zona pellucida,** the membranous structure surrounding the ovum

(3) **penetration** of the zona pellucida and the acrosome reaction

(4) **adherence** of the sperm head to the cell membrane of the ovum, with breakdown of the area of fusion and release of the sperm nucleus into the cytoplasm of the ovum

- Various enzymes are released, including the trypsin-like protease **acrosin.**

- Acrosin facilitates but is not required for the penetration of the sperm through the zona pellucida.

- Fusion to the ovum membrane is mediated by **fertilin,** a protein on the surface of the sperm head that resembles the viral fusion proteins which permit viruses to attack cells.

- The fusion provides the signal that initiates development.

- In addition, the fusion sets off a reduction in the membrane potential of the ovum that prevents polyspermy, the fertilization of the ovum by more than one sperm.

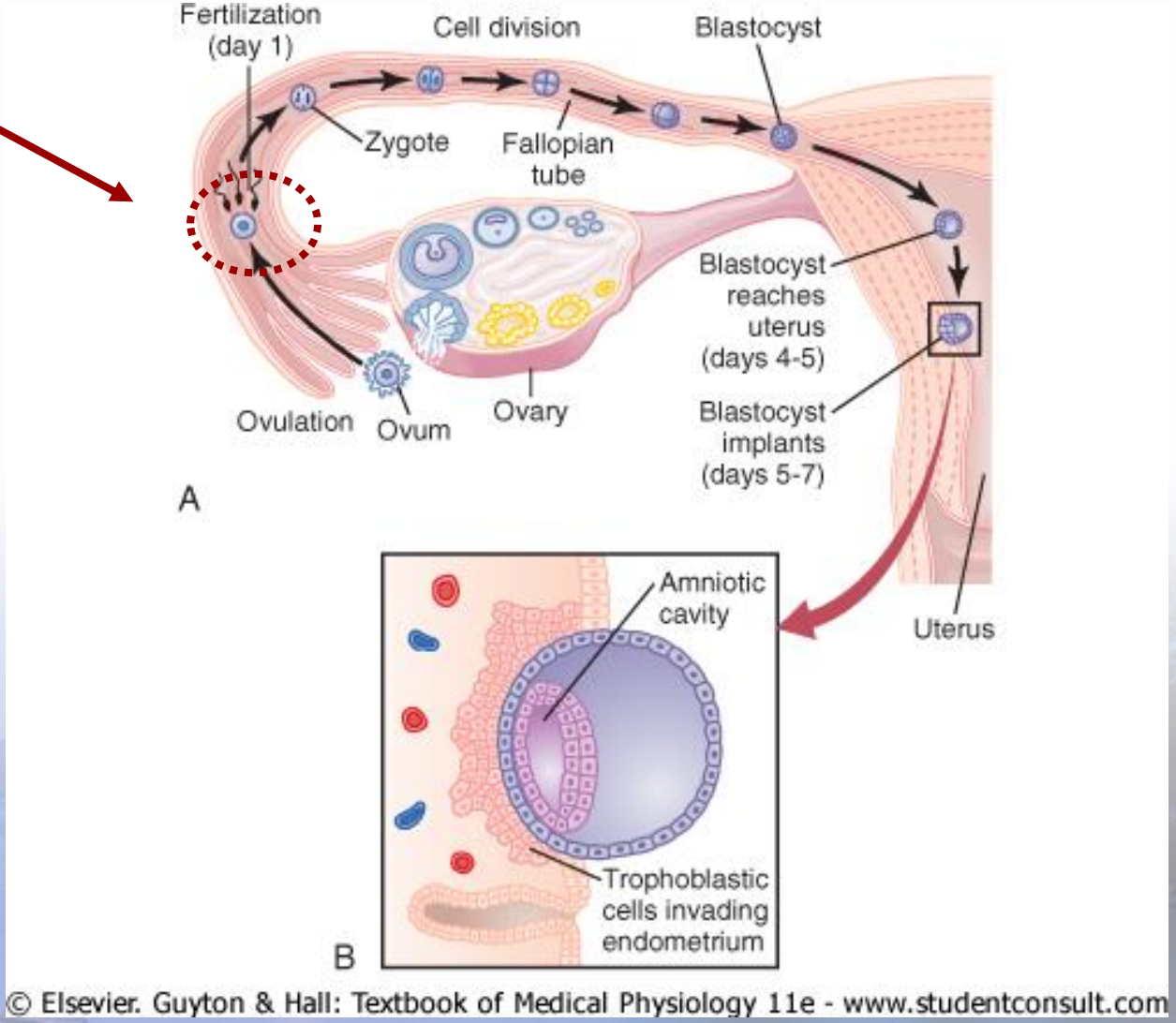
- This transient potential change is followed by a structural change in the zona pellucida that provides protection against polyspermy on a more long-term basis.

Fertilization

Fertilization in the ampulle of the FT.

- Prostaglandins
- Oxytocin

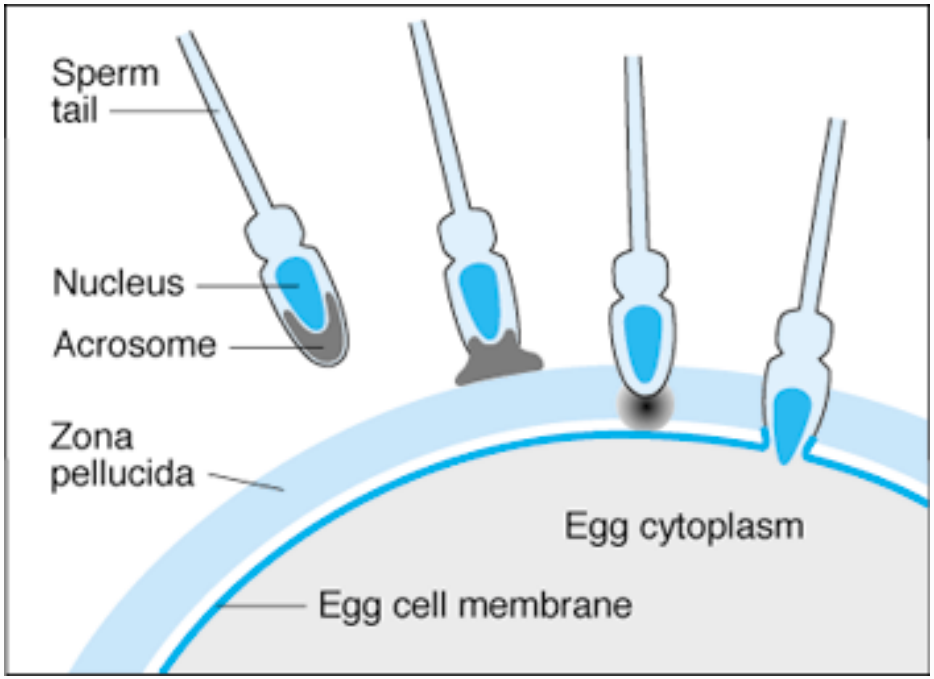
Ectopic (extrauterine) gravidity



Capacitation

- Freshly ejaculated sperm cannot immediately penetrate an egg.
- To bind to and penetrate the zona pellucida, the sperm must undergo **capacitation,**
- an irreversible process that involves an increase in sperm motility, the removal of surface proteins, a loss of lipids, and merging of the acrosomal and plasma membranes of the sperm head.
- The uniting of these sperm membranes and change in acrosomal structure is called the **acrosome reaction.**

- The reaction occurs when the sperm cell binds to the zona pellucida of the egg.
- It involves a redistribution of membrane constituents, increased membrane fluidity, and a rise in calcium permeability.
- Capacitation takes place along the female genital tract and lasts 1 hour to several hours.
- Sperm can be capacitated in a chemically defined medium, a fact that has enabled in vitro fertilization



- Sperms are attracted to the ovum,
- bind to the zona pellucida,
- release acrosomal enzymes,
- penetrate the zona pellucida
- fuse with the membrane of the ovum, releasing the sperm nucleus into its cytoplasm.

- The developing embryo, **blastocyst,** moves down the tube into the uterus.
- Takes about 3 days - blastocyst reaches the 8- or 16-cell stage.
- Blastocyst surrounded by an outer **syncytiotrophoblast,** and an inner **cytotrophoblast**
- The syncytiotrophoblast erodes the endometrium, and the blastocyst burrows into it **(implantation).**
- The implantation site is on dorsal wall of the uterus.
- A placenta then develops, and the trophoblast remains associated with it.

- At the time of implantation, the trophoblast cells of the early embryonic placenta produce a hormone, **human chorionic gonadotropin (hCG)**,

- This hormone signals the ovary to continue to produce progesterone, the major hormone required for the maintenance of pregnancy.

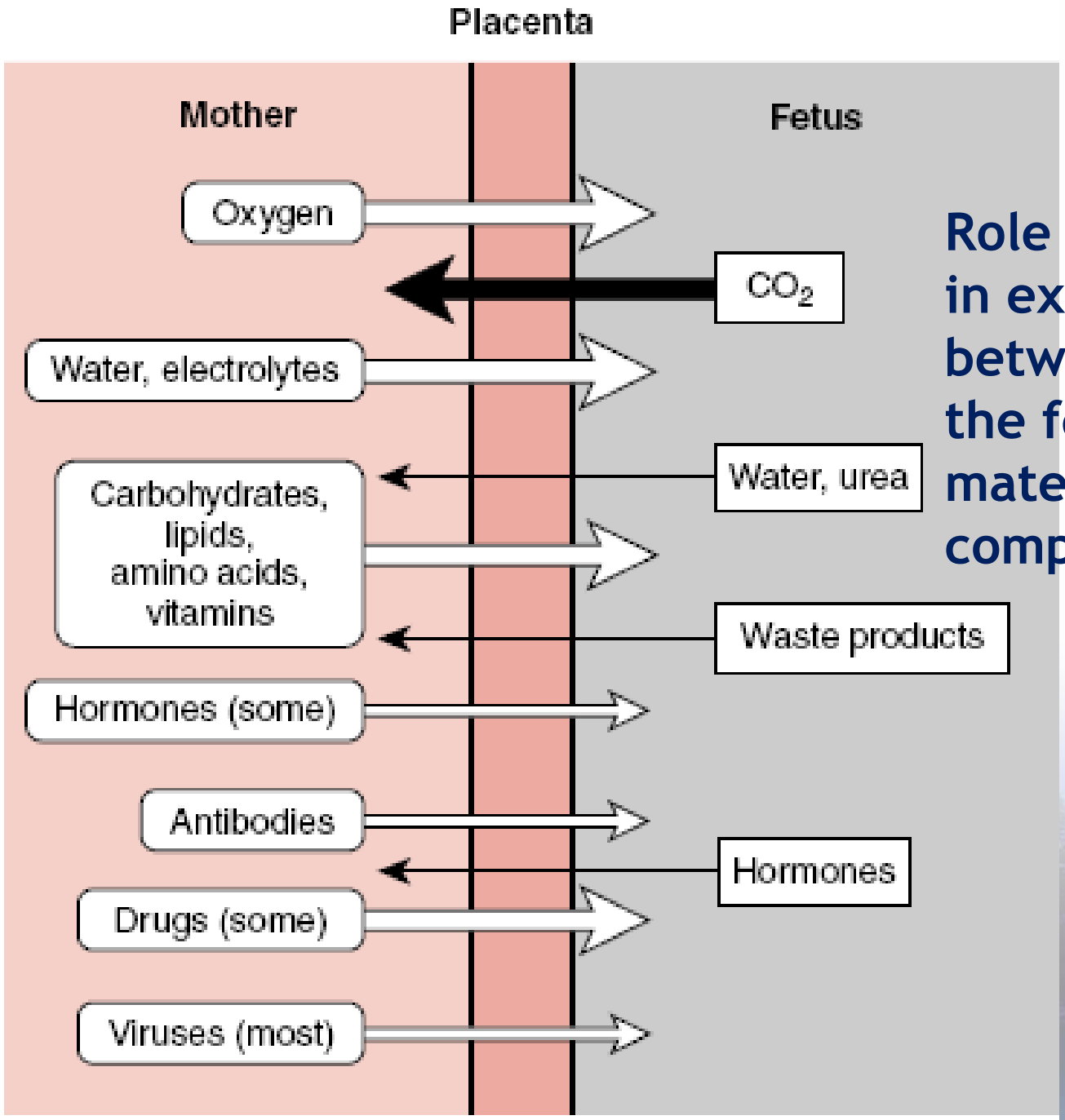
- In humans, the placenta takes over the function of the corpus luteum after the sixth week of pregnancy.
- The function of the corpus luteum begins to decline after 8 weeks of pregnancy, but it persists throughout pregnancy.
- hCG secretion decreases after an initial marked rise, but estrogen and progesterone secretion increase until just before parturition

- the corpus luteum enlarges in response to stimulation by **human chorionic gonadotropin (hCG).**
- The enlarged **corpus luteum of pregnancy** secretes estrogens, progesterone, and relaxin.
- Relaxin helps maintain pregnancy by inhibiting myometrial contractions.

Major functions of the placenta

- Delivery of nutrients to the fetus and the removal of its waste products.
- Oxygen diffuses from maternal blood to the fetal blood down a gradient of 60 to 70 mm Hg.
- The oxygen transporting capacity of fetal blood is enhanced by **fetal hemoglobin, which has a high affinity for oxygen**.
- The PCO_2 of fetal arterial blood is 2 to 3 mm Hg higher than that of maternal blood, allowing the diffusion of CO_2 toward the maternal compartment.

- Transport of nutrients and hormones,
- Removal of waste products,.
- Large proteins, - polypeptide hormones, do not readily cross the placenta, whereas the lipid-soluble steroids pass through quite easily.
- The **blood-placental barrier allows** the transfer of some immunoglobulins, viruses, and drugs from the mother to the fetus



Role of the placenta in exchanges between the fetal and maternal compartments.

Diffusion of Oxygen Through the Placental Membrane

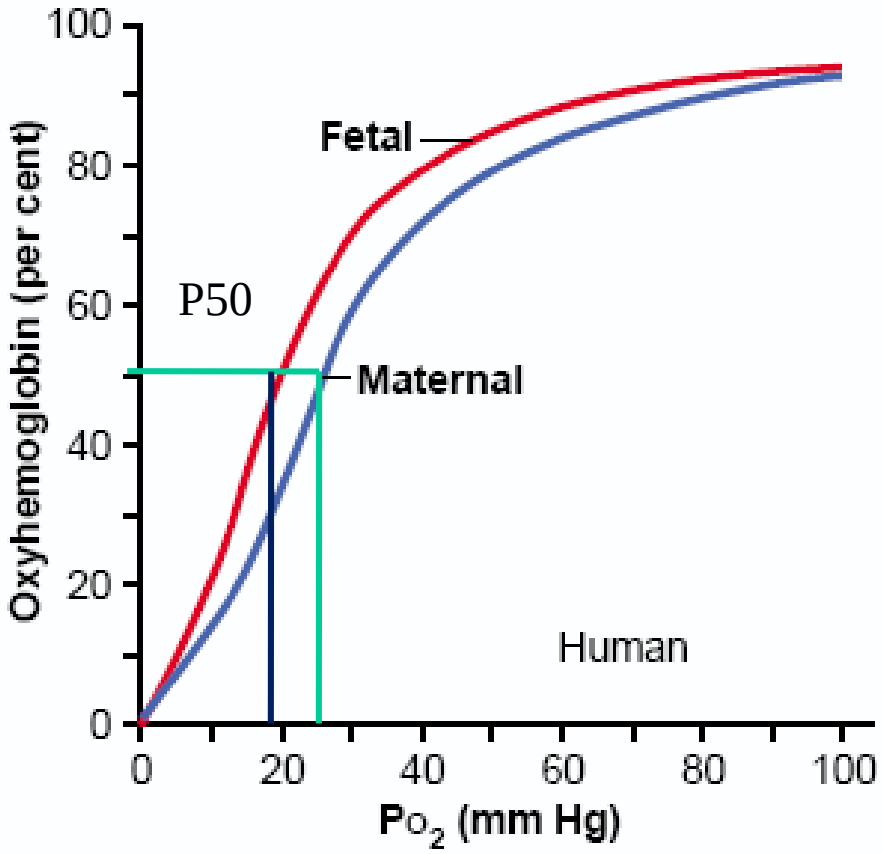
- **Simple diffusion**

- mean PO_2 of maternal blood = 50 mm Hg, the mean PO_2 in fetal blood = 30 mm Hg.

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

Reasons why fetal blood transports oxygen to the fetal tissues efficiently

- **1. Presence of Fetal hemoglobin**
- 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 maternal hemoglobin can.



Fetal blood can carry a greater quantity of oxygen than can maternal blood for a given blood PO_2.

2. **Hemoglobin concentration of fetal blood**

- is about 50 % greater than that of the mother
- Larger amount of oxygen transported to the fetal tissues.

3. the Bohr effect

- Hemoglobin can carry more oxygen at a low PCO_2 (and high pH) than it can at a high PCO_2 (and low pH).
- The fetal blood entering the placenta carries large amounts of CO_2, but much of this CO_2 diffuses from the fetal blood into the maternal blood.
- Loss of the CO_2 makes the fetal blood more alkaline and carry more oxygen, whereas the increased CO_2 in the maternal blood makes it more acidic and carry less oxygen.

- The PCO2 of the fetal blood is 2 to 3 mm Hg higher than that of the maternal blood.

- This small pressure gradient for CO_2 across the membrane allows adequate diffusion of CO_2, because CO_2 is very soluble in the placental membrane

- CO_2 diffuses 20 times as rapidly as oxygen.

- These changes cause the capacity of fetal blood to combine with oxygen to increase and that of maternal blood to decrease.

- This forces still more oxygen from the maternal blood, while enhancing oxygen uptake by the fetal blood.

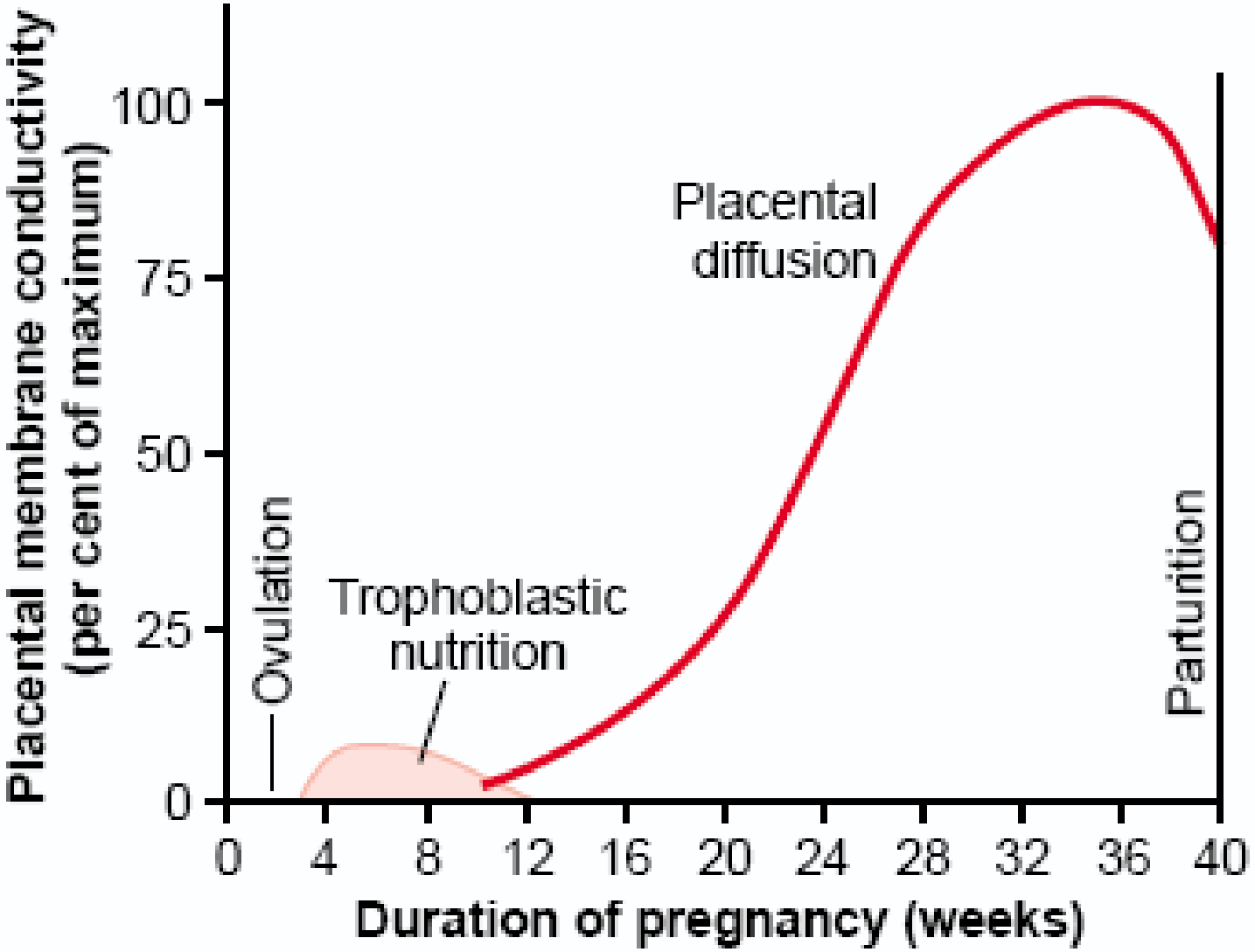
- Thus, the Bohr shift operates in one direction in the maternal blood and in the other direction in the fetal blood.

- These two effects make the Bohr shift twice as important here as it is for oxygen exchange in the lungs

- Therefore, it is called the ***double Bohr effect.***

Early Nutrition of the Embryo

- when the embryo implants in the endometrium, the continued secretion of progesterone causes the endometrial cells to swell further and to store even more nutrients.
- These cells are now called **decidual cells**, and the total mass of cells is called the decidua.
- this trophoblastic period of nutrition, which gradually gives way to placental nutrition.


Placental membrane conductivity (per cent of maximum)
100
75
50
25
0
Placental diffusion
Ovulation
Trophoblastic nutrition
Parturition
0
4
8
12
16
20
24
28
32
36
40
Duration of pregnancy (weeks)

Hormonal Factors in Pregnancy

- In pregnancy, the placenta forms
  - ***human chorionic gonadotropin hCG,***
  - ***estrogens,***
  - ***progesterone,***
  - ***human chorionic somatomammotropin hCS,***

Fetoplacental Unit

- The fetus and the placenta interact in the formation of steroid hormones.
- The placenta synthesizes pregnenolone and progesterone from cholesterol.
- Some of the progesterone enters the fetal circulation and provides the substrate for the formation of cortisol and corticosterone in the fetal adrenal

- Some of the pregnenolone enters the fetus

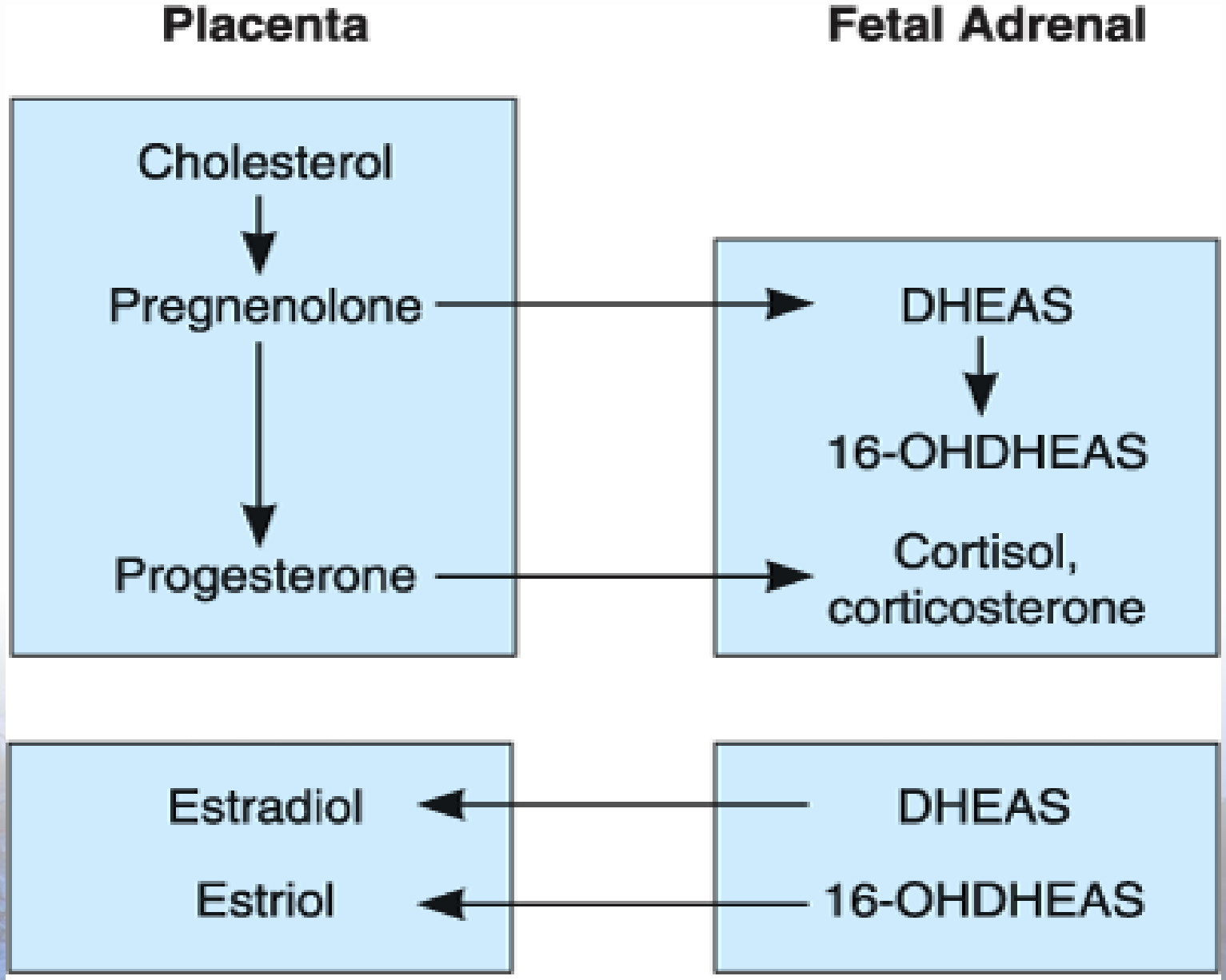
- Along with pregnenolone synthesized in the fetal liver, forms the substrate for the formation of
  - dehydroepiandrosterone sulfate (DHEAS) and
  - 16-hydroxydehydroepiandrosterone sulfate (16-OHDHEAS) in the fetal adrenal.

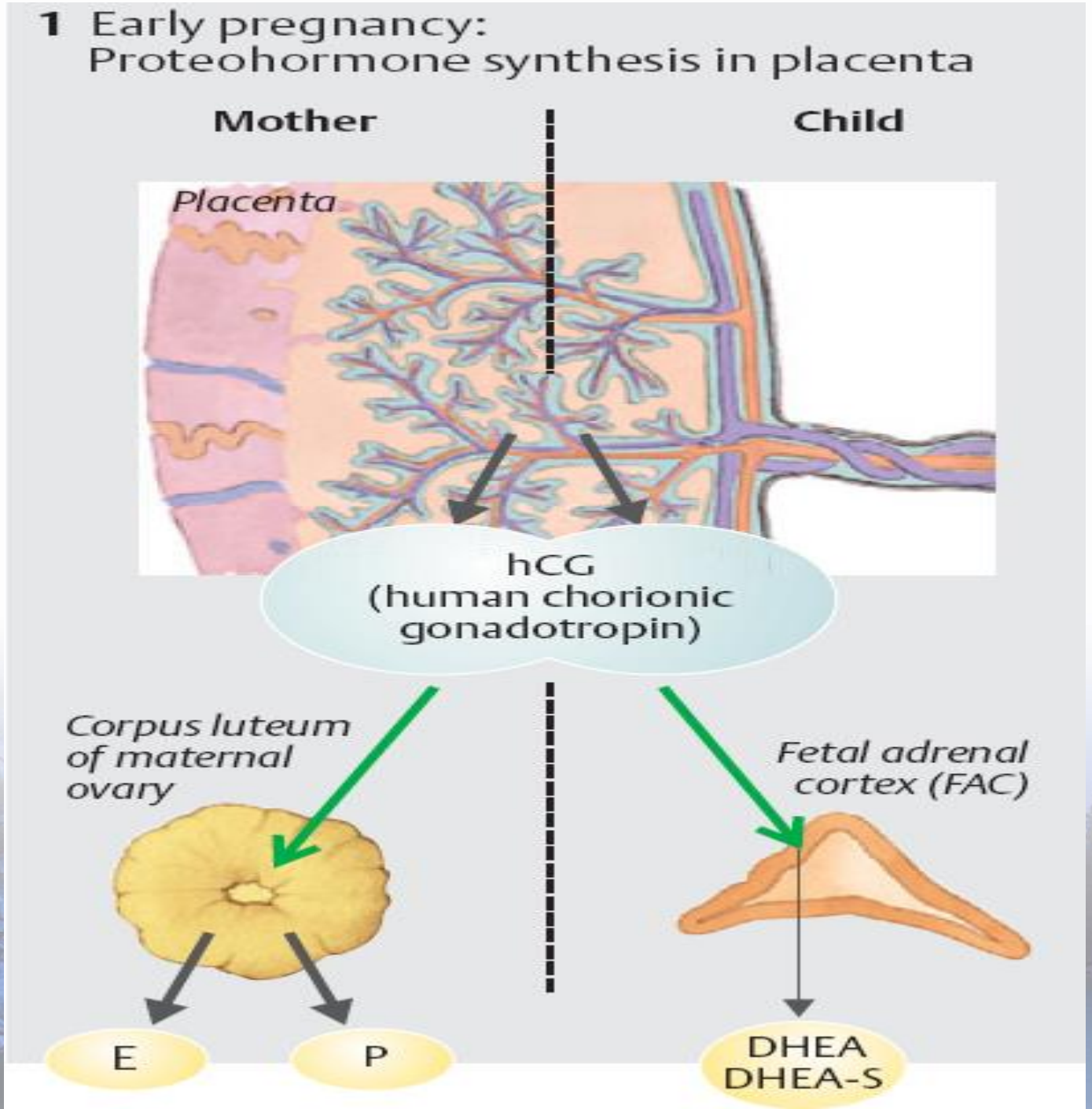
- Some 16-hydroxylation also occurs in the fetal liver.

- DHEAS and 16-OHDHEAS are transported back to the placenta, where DHEAS forms estradiol and 16-OHDHEAS forms estriol.

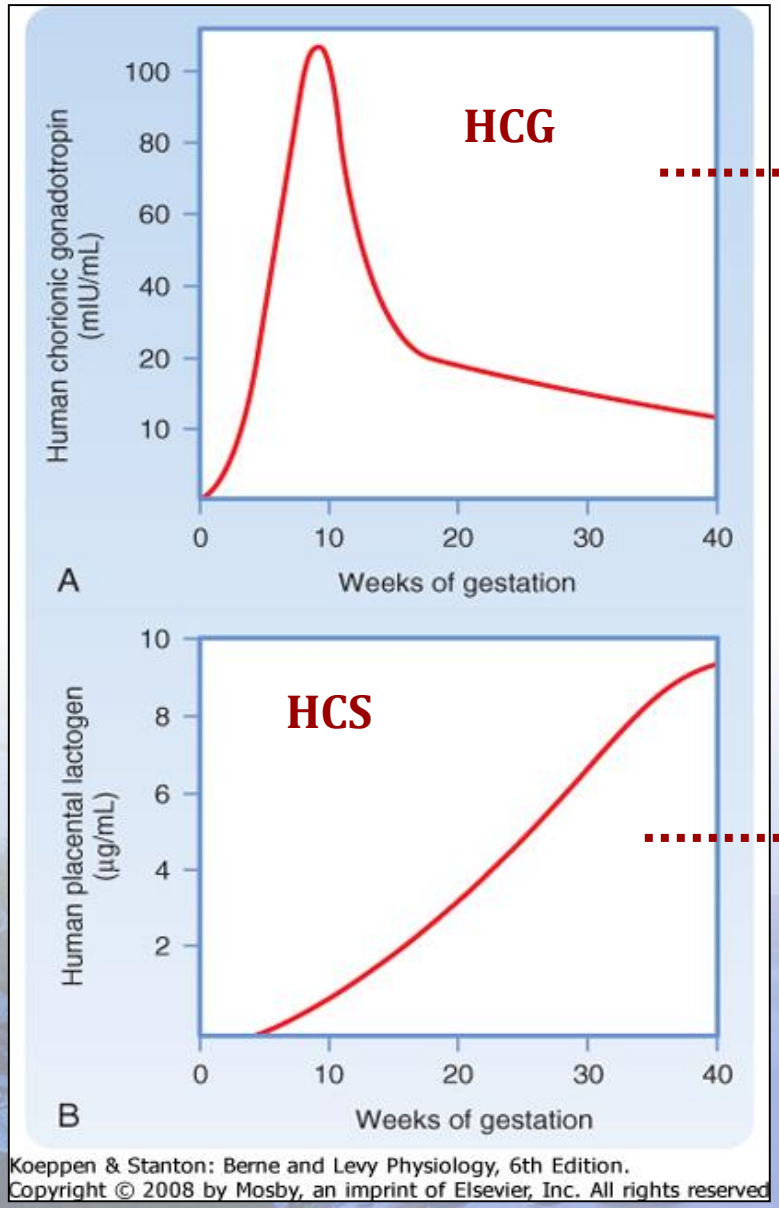
- The principal estrogen formed is estriol,

- Since fetal 16-OHDHEAS is the principal substrate for the estrogens, the urinary estriol excretion of the mother can be monitored as an index of the state of the fetus.




1 Early pregnancy:
Proteohormone synthesis in placenta
Mother
Child
Placenta
hCG
(human chorionic
gonadotropin)
Corpus luteum
of maternal
ovary
Fetal adrenal
cortex (FAC)
E
P
DHEA
DHEA-S

Hormonal changes



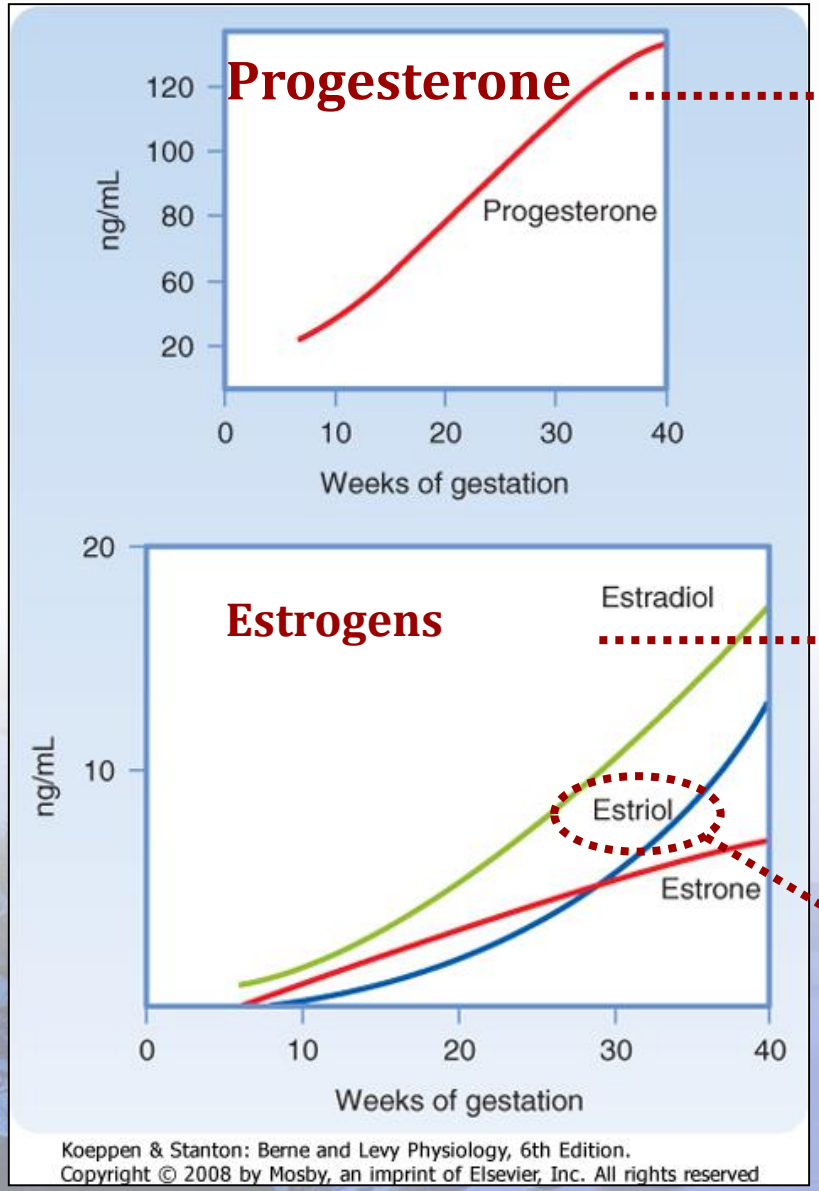
Human Chorionic Gonadotropin

- prevent involution of CL (pregesterone, estrogen)
- effect on the testes of male fetus - development of sex organs

Human Chorionic Somatomammotropin

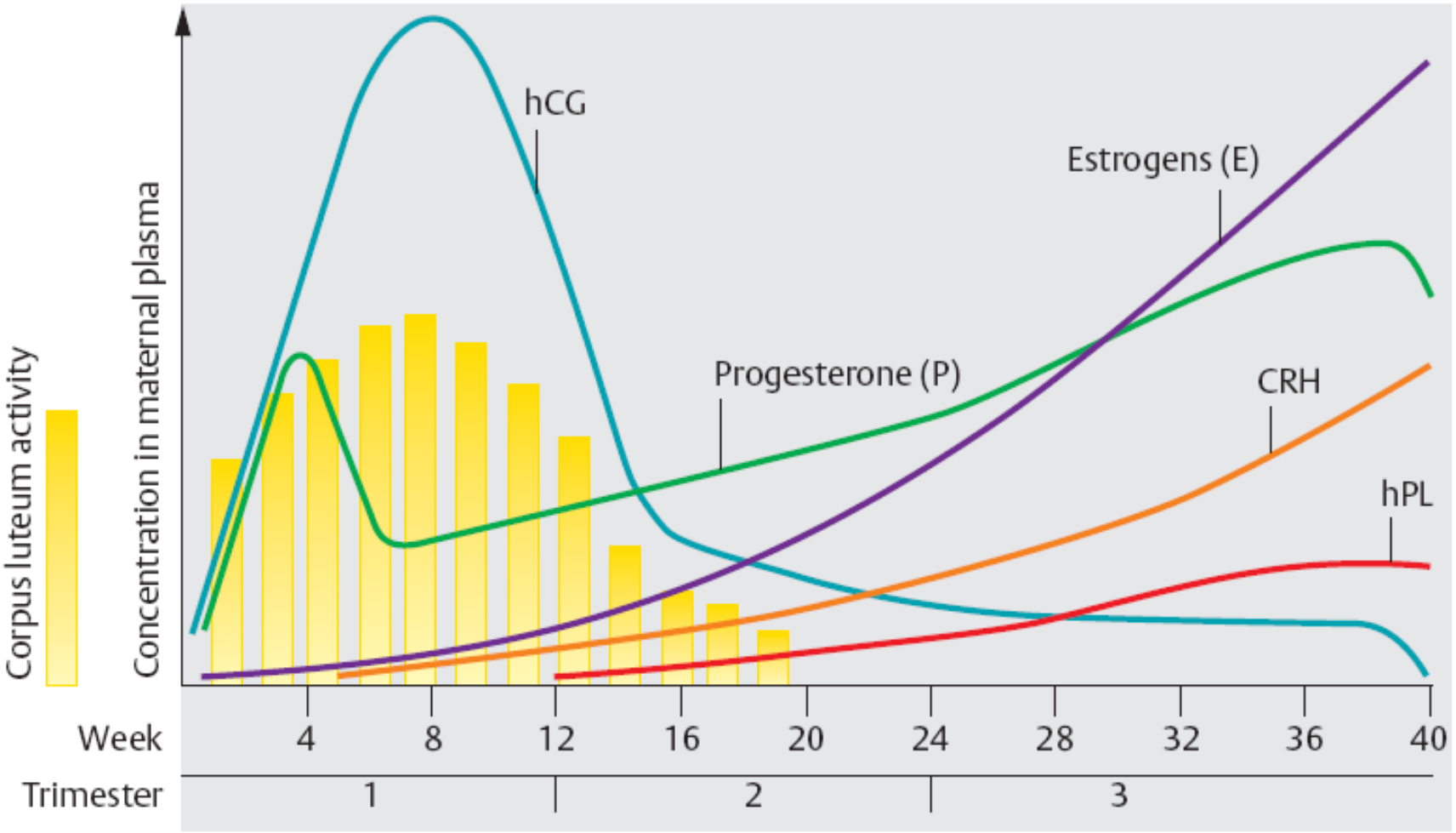
- effect on latation (HPL) ?
- growth hormone effects
- decreases insulin sensitivity - more glucose for the fetus
- low levels - placental insufficiency.

Hormonal changes



- development of decidual cells
- decreases uterus contractility
- preparation for the lactation
- enlargement of uterus
- breasts development
- relaxation of ligments
- estriol level - indicator of vitality of the fetus

B. Hormone concentrations in plasma during pregnancy



hCG

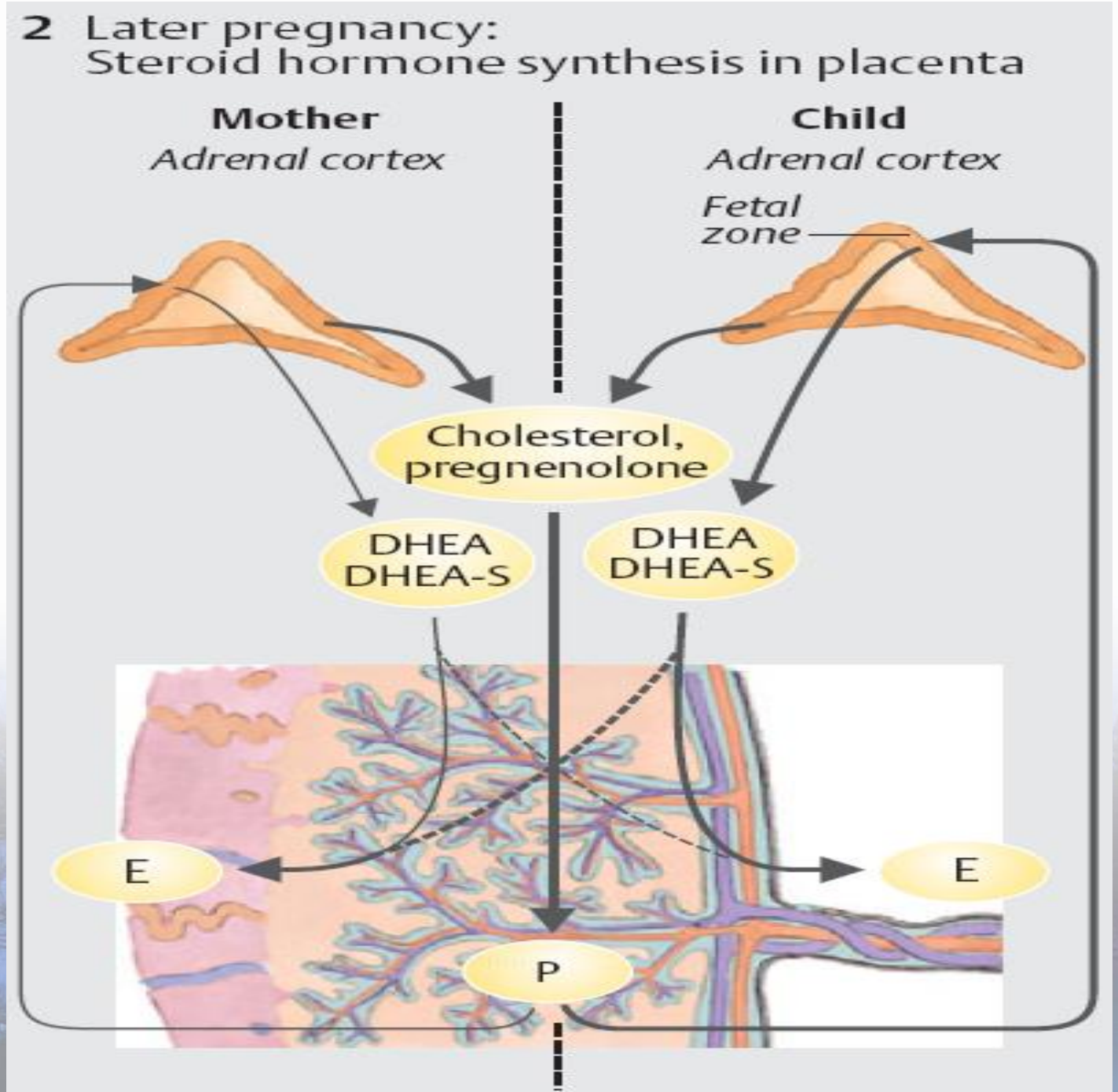
- hCG is produced by the syncytiotrophoblast.
- It can sometimes be detected in the urine as early as 14 days after conception.
- It appears to act on the same receptor as LH.

- prevents involution of the corpus luteum
- causes the corpus luteum to secrete large quantities of progesterone and estrogens—for the next few months.
- They prevent menstruation and cause the endometrium to store nutrients
- Decidual cells are formed—greatly swollen and nutritious—at about the time of implantation.

Placental estrogens

- Toward the end of pregnancy, the daily production of placental estrogens increases to about 30 times normal

- The estrogens secreted by the placenta are not synthesized newly from basic substrates in the placenta.
- Instead, they are formed from androgenic steroid compounds, dehydroepiandrosterone (DHEA) dehydroepiandrosterone sulphate and 16- hydroxydehydroepiandrosterone, formed both in the mother's and fetal adrenal glands
- They are transported by the blood to the placenta and converted by the trophoblast cells into estradiol, estrone, and estriol.


2 Later pregnancy:
Steroid hormone synthesis in placenta
Mother
Adrenal cortex
Child
Adrenal cortex
Fetal zone
Cholesterol, pregnenolone
DHEA DHEA-S
DHEA DHEA-S
E
E
P

Function of Estrogen in Pregnancy

(1) enlargement of the mother's uterus,

(2) enlargement of the mother's breasts and growth of the breast ductal structure,

(3) enlargement of the mother's female external genitalia.

(4) the sacroiliac joints and the symphysis pubis become elastic. These changes allow easier passage of the fetus through the birth canal

Functions of progesterone secreted by the placenta

- Decidual cells develop
- Decreases the contractility of the pregnant uterus
- Increases the secretions of the mother's fallopian tubes and uterus
- Helps estrogen prepare the mother's breasts for lactation

hCS – human chorionic somatomammptropin

- The syncytiotrophoblast also secretes a protein hormone that is lactogenic and has a small amount of growth-stimulating activity.

- This hormone is **human chorionic somatomammotropin (hCS).**

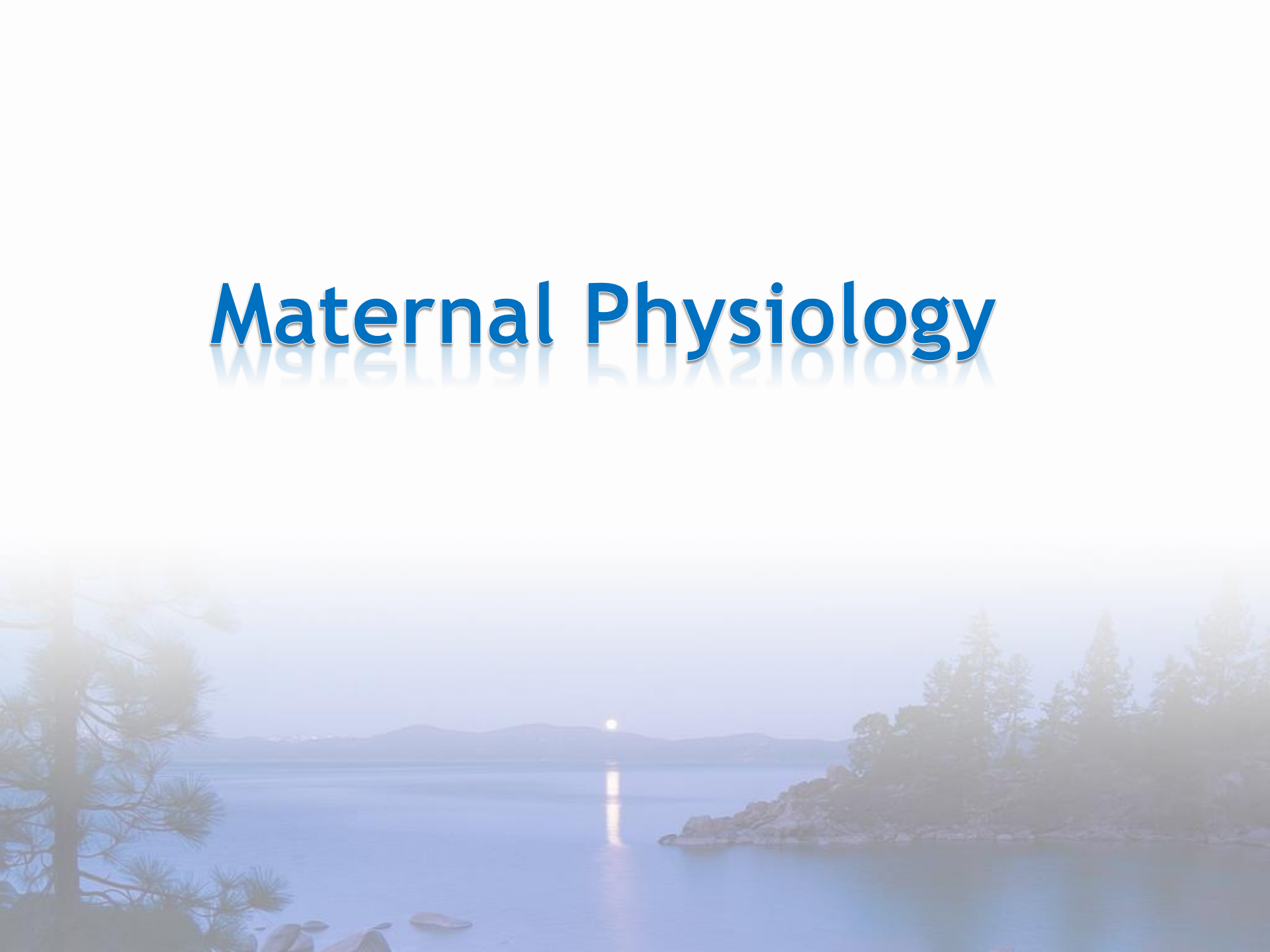
- The structure of hCS is very similar to that of human growth hormone

- hCS has most of the actions of growth hormone and functions as a "maternal growth hormone of pregnancy" to bring about
  - nitrogen, potassium, and calcium retention,
  - lipolysis,
  - decreased glucose utilization.
- These latter two actions divert glucose to the fetus.
- The amount of hCS secreted is proportionate to the size of the placenta, which normally weighs about one-sixth as much as the fetus,
- Low hCS levels are a sign of placental insufficiency.

Alpha-fetoprotein (AFP)

- Derived from embryonic endodermal tissues
- Highest concentration in amniotic fluid
- Lesser amounts in maternal peripheral blood
- An index of fetal wellbeing

Maternal Physiology



Maternal Physiology

- Basal metabolic rate increases 15%
- Cardiac output transiently increases 30-40%
- Blood volume increases 30%
- O_2 utilization increases 20%
- Ventilation increases 50%
- Renal tubule reabsorption increased 50%
- Glomerular filtration rate increased 50%

Weight Gain and Pregnancy

- Average – 12.5 kg, can be as much as 17 Kg
- Fetus – 3.4 kg
- Amniotic fluid – 0.8 kg
- Extraembryonic fluid/tissues – 7 kg
- Uterus – 1 kg
- Breasts – 0.8 kg
- Body fluid – 6 lbs
- Fat accumulation – 1.5 kg

Water retention in extracellular fluid

- ICF – 550 ml
- ECF
  - Plasma – 900 ml
  - Interstitial fluid – 1850 ml
- Total – 3300 ml

- Corresponding amounts of sodium are also retained.
- Probably due to high concentrations of sex steroids

Metabolic changes

- BMR increases between 10-25 %. Probably due to metabolism of fetus and supporting tissues
- Total need for calories increases by 80,000 kcal

Carbohydrate metabolism

- Renal threshold for glucose is lowered and glucose appears in the urine – probably the result of increased GFR
- High protein intake needed

Changes in the blood

- Total blood volume increases by about 30%
- The uterine wall and maternal blood spaces contain about 800 ml of blood
- Increase in blood volume supplies this need

Changes in the blood

- blood volume increases by ~ 30%,
  - increase in plasma ~ 50% due to aldosterone & oestrogen
  - increase in RBC mass ~ 30%
  - decreased [Hb] & haematocrit
- Therefore, blood becomes more dilute
- Iron supplements may be needed for those with poor iron reserves and poor diet

Changes in the blood

- a hypercoagulable state exists due to,
  - an increase in clotting factors I, VII, VIII, IX, X, and fibrinogen
  - decrease in antithrombin III

Changes in the circulation

- **Cardiac output** - rises from 4.5 L/min to 6 L/min during the first 10 weeks of pregnancy & remain at this level throughout pregnancy

- **Systolic blood pressure** is unaltered but diastolic blood pressure falls in the first and second trimesters – returns to non-pregnant levels

- **Pulse rate** – rises between 8-10 beats/min
- Therefore stroke volume has to rise by 70-80 ml
- Slight extra work

Arteriovenous shunt

- Across uterine circulation
- Increase in renal blood flow
- Dilatation of peripheral blood vessels
- Hands and feet are warm , skin capillaries dilated

- Enlarged uterus interferes with venous return from the legs
- Venous stasis and oedema of legs
- Faintness when lying on the back, haemorrhoids, varicose veins

Uterine Circulation

- During pregnancy, blood flow increases rapidly producing up to ~ 20 fold increase

- As the size, and requirements of the foetus increase >> than blood flow during pregnancy, the O2 extraction ratio increases progressively with pregnancy

Changes in the respiratory system

- Pulmonary ventilation increases by 40% as a result of increased tidal volume
- Overbreathing leads to a reduction in PCO_2
- Low PCO_2 leads to a sensation of dyspnoea

Changes in the alimentary tract

- Nausea (morning sickness)
- Increase in appetite and thirst
- Heartburn – relaxation of LOS
- Prolonged gastric emptying time

Changes in the urinary tract

- Progressive increase in GFR and RPF – starting in early pregnancy and reaching 50% at term
- Water retention 7.5 L, with 950 mmol Na^+
- Largely due to increased steroids, aldosterone, angiotensin II

Changes in the urinary tract

- Progressive dilatation of ureters upto level of pelvic brim
- Loss of muscle tone - progesterone

Immune reactivity

- Fetus is an allograft foreign to the mother

- Why does the mother's immune system not reject the fetus?

Endocrine functions

- Earliest changes are increased levels of,
  - a. oestrogen, b. progesterone, c. hCG
- There are increases in the size of,
  - a. thyroid - remain euthyroid
  - b. parathyroid - PTH rises ® increased Vit.D3
    - increased Ca++ absorption
    - decreased Ca++ excretion
    - plasma [Ca++] remains normal, the increase supplying foetus
  - c. anterior pituitary ➔ ACTH & PRL
  - d. adrenals ➔ cortisol & aldosterone

Cutaneous changes

- **Increased pigmentation**
- **Purple stria: striae gravidarum**

Renal changes

- **Increased frequency.**
- **Slight albuminuria.**
- **Sodium & water retention.**