YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 10 - Physiology

Lec. Title : Pregnancy (Part 1)

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Physiology of Pregnancy part 1

المحاضرة بتبدأ في كوستانزو من صفحة 478
وفي بيرني آند ليفاي من صفحة 816
وفي غايتون من صفحة 1055 تشابتر 83
دعواتكم للأهل في فلسطين وغزة وإلنا كمان, كل الحُبّ ...

كل شخص من أهل الكتاب سواء كان مسلم أو مسيحي أو يهودي هو مسؤول تمامًا عن محاربة الصهيونية..

دولة الاحتلال ما قامت لأنه في معبد ضائع ، اليهود والمسيحيين والمسلمين بيعرفوا هالشي كلٌّ من كتابه.. دولة الاحتلال قامت بهدف الاحتلال فقط وأكبر دليل جرائمها وانتهاكها للأديان والأعراض والممتلكات وحيات الكبار والأطفال.. كلكم بتعرفوا عربي وانجليزي ، اعملوا مسؤوليتكم وانشروا الحقيقة ، فلسطين "أرض المحشر كما اتفقت الأديان الثلاث" بحاجة لكل كلمة... وما تنسوا أهلها من دعاؤكم..

Pregnancy

- The reproductive system of women undergoes dramatic changes during pregnancy.
- The production of gonadotropin and gonadal steroids is **switched from** the maternal hypothalamic-pituitary-ovarian axis(Corpus luteum), which is *strongly repressed during pregnancy*, **to t**he fetal placenta.
- The **endocrine function of fetal placental tissue** is dominant that:

❖ (1) maintains a **quiescent gravid uterus(**it is relaxed and there is no contraction.)

❖ (2) alters ma**ternal physiology** to ensure **fetal** nutrition in utero

❖ (3) **alters maternal pituitary function** and **mammary gland development** to ensure **ongoing** fetal nutrition after birth,

❖ (4) determines the **time of labor and delivery** (also called **parturition**).

❖ (5) The placenta also plays an important role in **fetal testosterone production and male differentiation** of the reproductive system before the fetal hypothalamus and pituitary develop into a functional axis.

Pregnancy

- If the ovum is fertilized by a sperm, the fertilized ovum begins to divide and will become the fetus.
- The period of development of the fetus is called **pregnancy or gestation,** which, in humans, lasts approximately **40 weeks. (38 weeks from ovulation and 40 weeks from the last menses)**
- Is characterized by steadily increasing levels of estrogen and progesterone. Their functions include:

1. Maintenance of the endometrium for the fetus
2. Suppression of ovarian follicular function (by inhibiting FSH and LH secretion)
3. Stimulation of breast development for lactation.

Events of early pregnancy

TABLE 1. Events of Early Pregnancy

Event	Days After Ovulation
Ovulation	0 day
Fertilization	1 day
Entrance of blastocyst into uterine cavity	4 days
Implantation	5 days
Formation of trophoblast and attachment to endometrium	6 days
Onset of trophoblast secretion of HCG	8 days
HCG "rescue" of corpus luteum	10 days

HCG, Human chorionic gonadotropin.

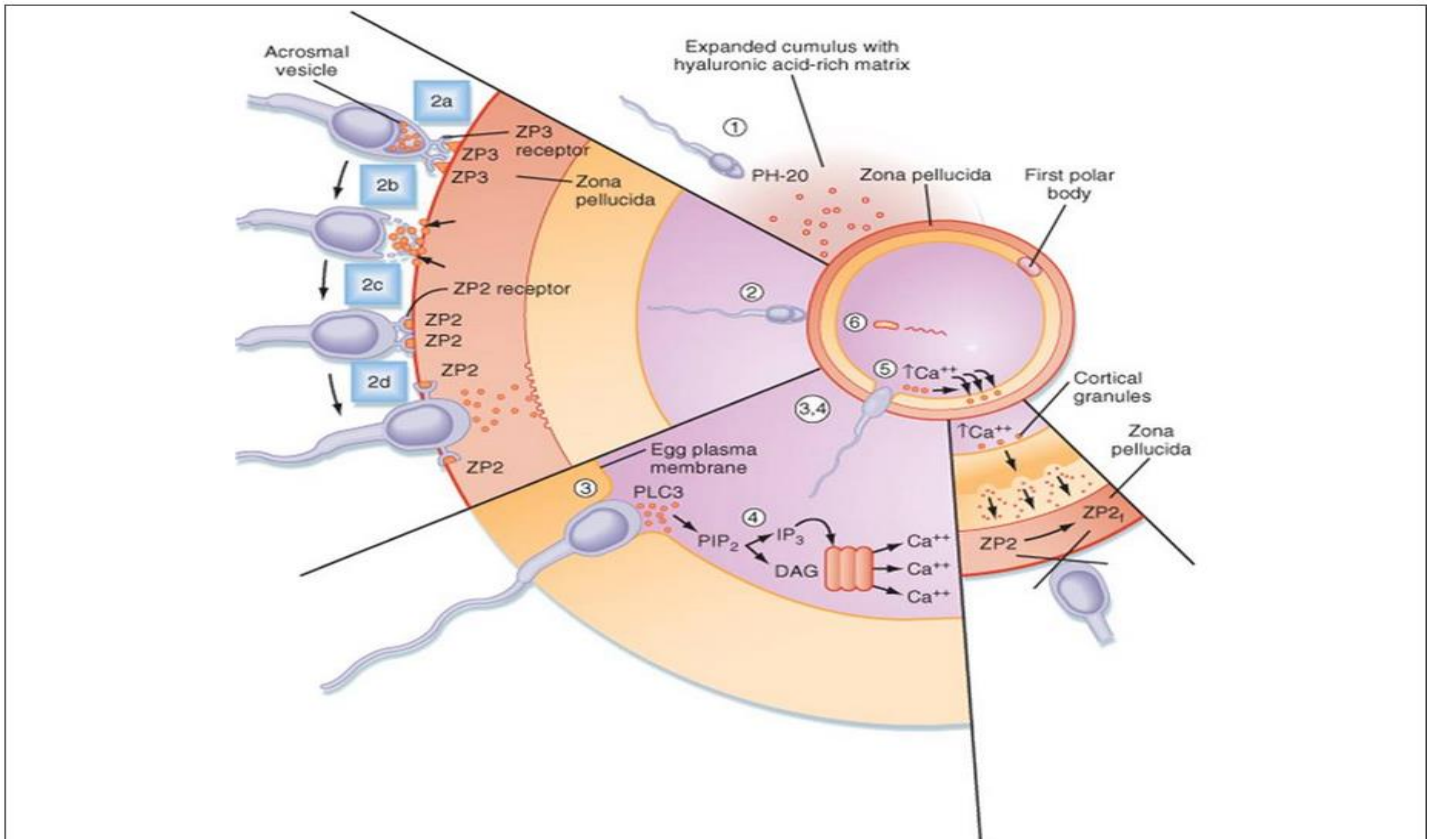
1. Fertilization

- Fertilization accomplishes both recombination of genetic material to form a new genetically distinct organism and initiation of events that begin embryonic development.
- **Fertilization** of the ovum takes place within 24 hours of ovulation, in a distal portion of the oviduct called the **ampulla.**
- Once a **sperm penetrates** the ovum, the **second polar body is extruded** and the **fertilized ovum begins to divide.**

From the figure in the next slide

- **Step 1:** Penetration of the expanded cumulus by the sperm. This involves **digestion** of the extracellular matrix of the cumulus by **a membrane hyaluronidase**, PH-20.
- **Step 2:** Penetration of the zona pellucida by the sperm. This involves **binding** of the sperm to the **zona protein ZP3** (step 2a), which induces release of acrosomal enzymes (called the **acrosomal reaction** (step 2b). The sperm **secondarily bind** to **another zona protein, ZP2** (step 2c), as the zona pellucida is **digested** and the **sperm swims through to the egg** (step 2d).
- **Step 3: Fusion** of the sperm and egg membrane takes place.

- **Step 4: A Ca++ signaling cascade** occurs.
- **Step 5:** The signaling cascade activates the exocytosis of enzyme-filled vesicles called cortical granules that reside in the outermost, or cortical, region of the unfertilized egg.
- The enzymes contained in the cortical granules are released to the outside of the egg upon **exocytosis**. These enzymes **modify both ZP2 and ZP3** of the zona pellucida such that **ZP2 can no longer bind acrosome reacted sperm**, and **ZP3 can no longer bind capacitated acrosome-intact sperm.** Thus **only one sperm usually enters the egg.**



- Occasionally, more than one sperm does enter the egg. This results in a **triploid cell** that is **unable to develop further**. Therefore prevention of polyspermy is critical for normal development of the fertilized egg.
- **Step 6:** The entire sperm enters the egg during fusion. The flagellum and mitochondria disintegrate, so m**ost of the mitochondrial DNA in cells is maternally derived**.
- Once inside the egg, **decondensation of the sperm DNA occurs**. A membrane called the **pronucleus forms around the sperm DNA** as the newly activated egg completes the second meiotic division.
- In mammalian eggs a large initial release of Ca++ is followed by a series of subsequent smaller Ca++ oscillations that can last for hours. A major consequence of this is that it "**wakes up"** the metabolically quiescent a pronucleus forms around the female chromosomes as well.
- A **centrosome** contributed by the *sperm* becomes a m**icrotubule organizing cente**r from which *microtubules extend until they contact the female pronucleus*.
- The male and female **DNA replicate as the two pronuclei are pulled together**. Once the pronuclei contact each other, the nuclear membranes break down, the chromosomes align on a common metaphase plate, and the **first cleavage occurs.**

Maturation and fertilization of the ovum

- After fertilization, 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.
- This transport is effected 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 fallopian tubes are lined with a rugged cryptoid surface that impedes passage of the ovum despite the fluid current.
- Also, 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**.

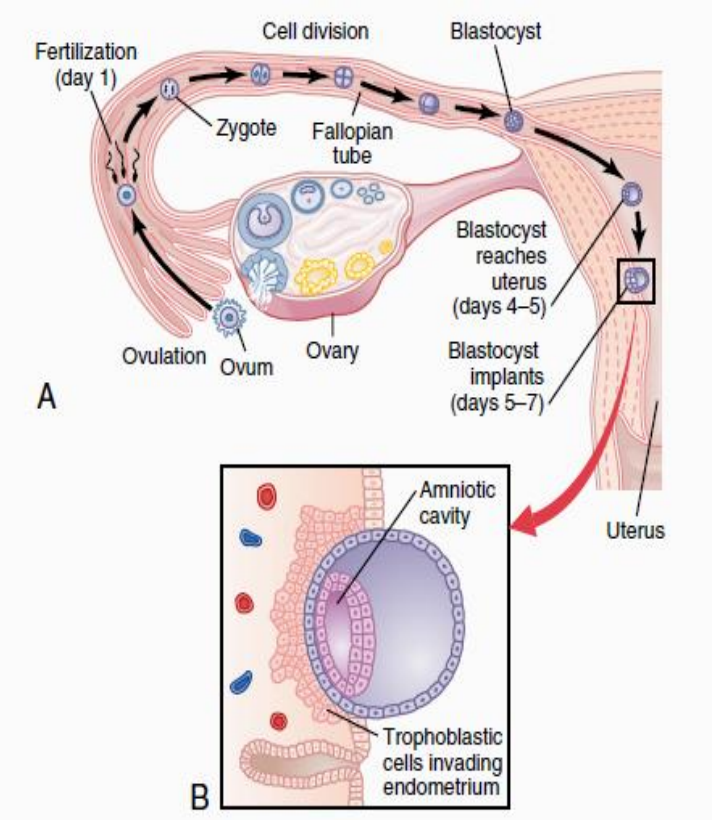


Figure 1 *A*, Ovulation, fertilization of the ovum in the fallopian tube, and implantation of the blastocyst in the uterus. *B*, Action of trophoblast cells in implantation of the blastocyst in the uterine endometrium.

Maturation and fertilization of the ovum

- After this time, the **rapidly increasing progesterone** secreted by the ovarian corpus luteum first **promotes increasing progesterone receptors** on the fallopian tube smooth muscle cells; then the progesterone activates the receptors, exerting **a tubular relaxing effect** that allows entry of the ovum into the uterus.
- This delayed transport of the fertilized ovum **allows several stages of cell division to occur** before the dividing ovum—now called a **blastocyst**, with about **100 cells—enters the uterus.**
- During this time, the fallopian tube secretory cells produce large quantities of secretions used for the **nutrition** of the developing blastocyst.

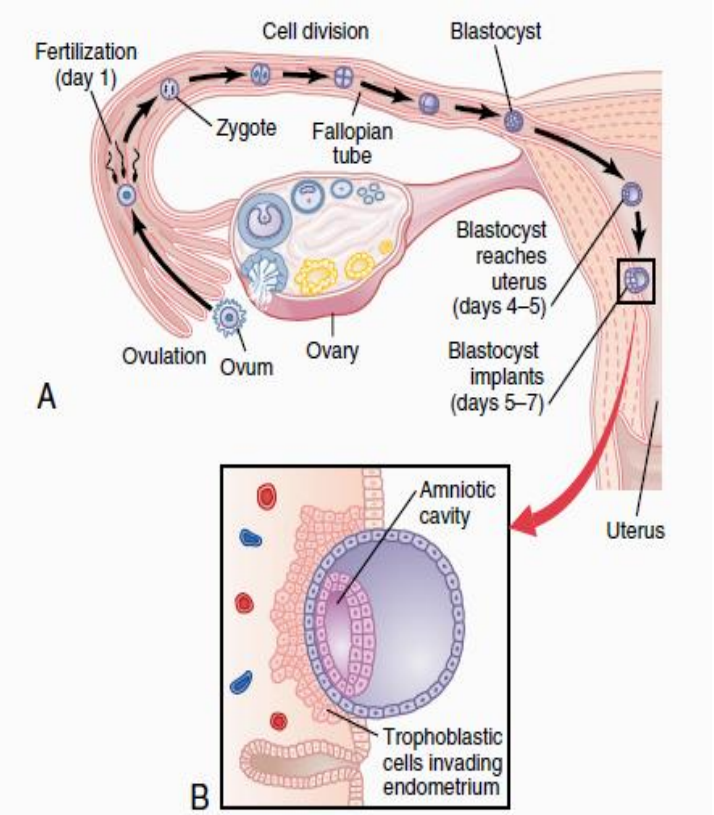
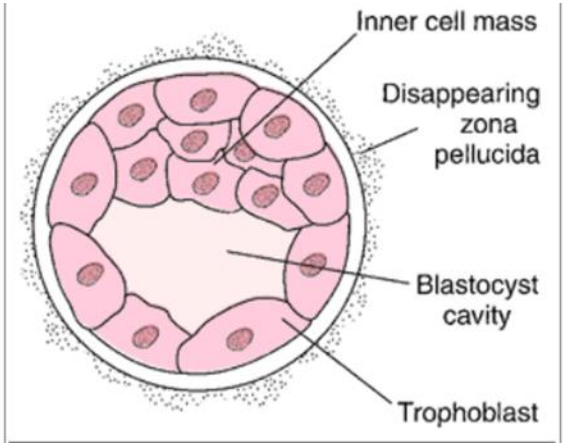


Figure 1 *A*, Ovulation, fertilization of the ovum in the fallopian tube, and implantation of the blastocyst in the uterus. *B*, Action of trophoblast cells in implantation of the blastocyst in the uterine endometrium.

2. Implantation

- The blastocyst floats freely in the uterine cavity for 1 day and then implants in the endometrium 5 days after ovulation.
- Zygotes are totipotent: gives rise to a complete human being/animal. They are also called "totipotent stem cells".
- The receptivity of the endometrium to the fertilized ovum is critically dependent on a **low estrogen/progesterone ratio** and corresponds to the period of highest progesterone output by the corpus luteum.
- At the time of implantation, the blastocyst consists of an i**nner mass** of cells, which will become the **fetus**, and an outer rim of cells called the **trophoblast.**
- The trophoblast invades the endometrium and forms an attachment to the maternal membranes. Thus the trophoblast contributes the ***fetal* portion of the placenta.**
- If you want to isolate the embryonic stem cells (pluripotent cells that give rise to everything except for the placenta etc…), do so by extracting them from the inner mass.



2. Implantation

- At the point of implantation, under stimulation by progesterone, the endometrium differentiates into a specialized layer of **decidual cells.** Eventually, the decidua will envelop the entire conceptus (= the embryo and its appendages or associated membranes).
- Trophoblastic cells proliferate and form the **syncytiotrophoblast**

Syncytiotrophoblasts:

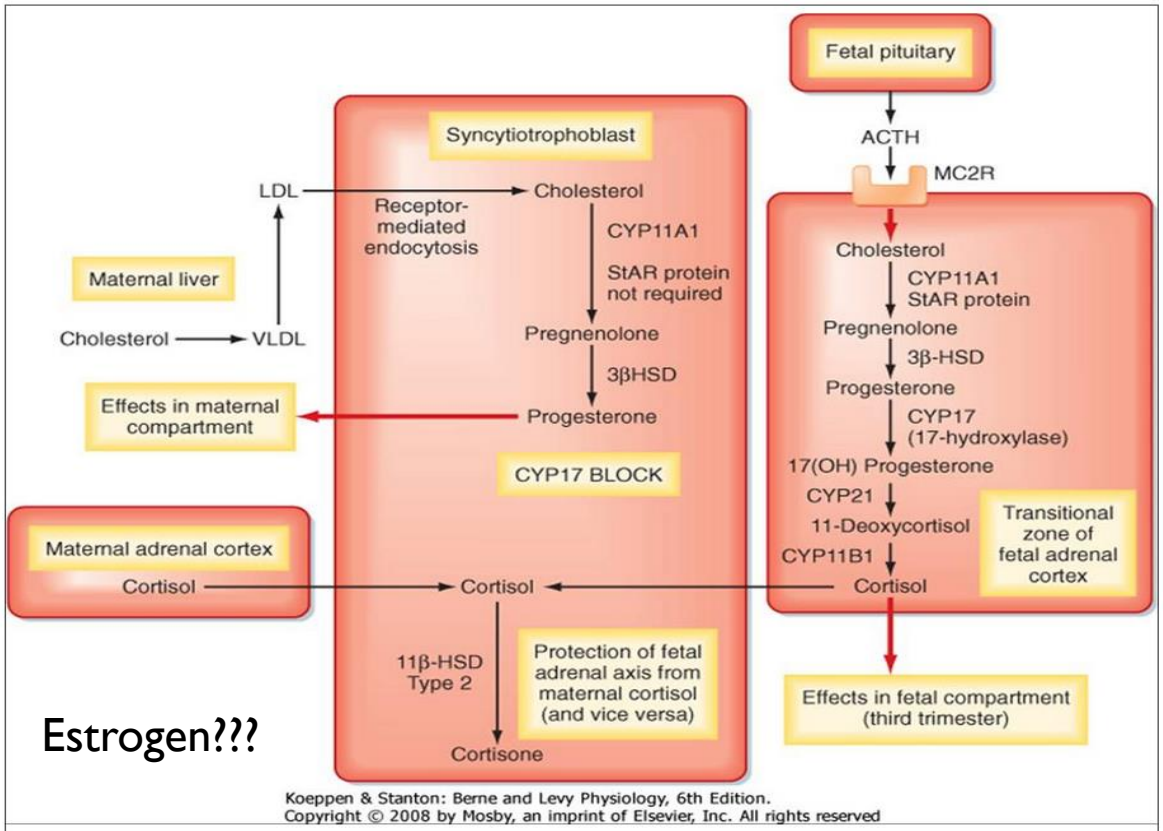
- Syncytiotrophoblasts initially perform three general types of function:

- **adhesive (**express adhesive surface proteins; i.e., **cadherins** & **integrins** that *bind to uterine surface epithelia*)
- **Invasive**
- **Endocrine:** with the *onset of implantation*, start **secreting the LH-like protein human chorionic gonadotropin HCG**, which *maintains the viability of the corpus luteum* and thus progesterone secretion. **By 10 weeks**, the syncytiotrophoblasts acquire the ability to *make progesterone at sufficient levels* to **maintain pregnancy independently of a corpus luteum.** Syncytiotrophoblasts produce several other hormones, as well as enzymes that modify hormones.)
-

2. Implantation

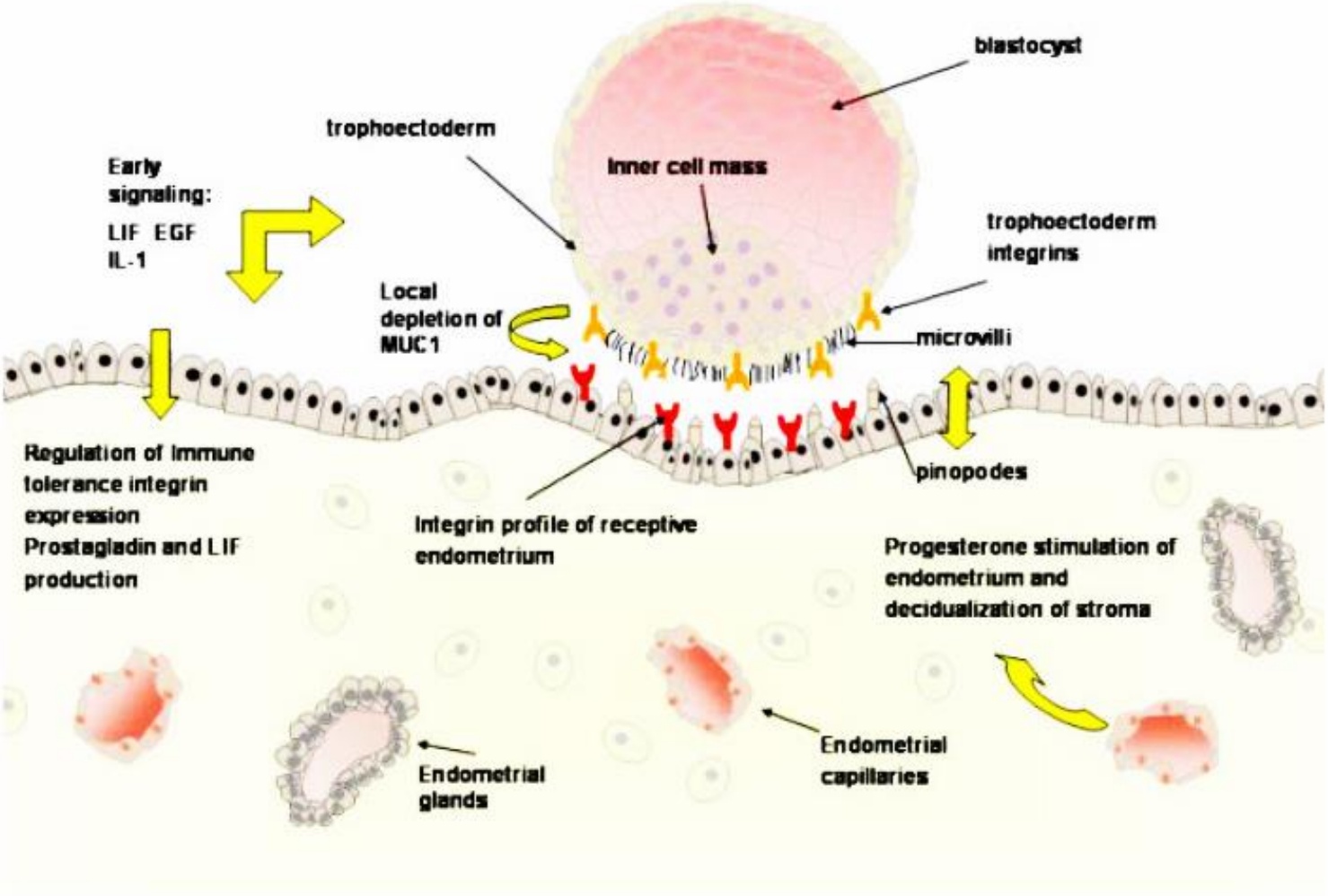
- **High levels of progesterone** :
  - Causes **angiogenesis**: *increases blood supply to the uterus.*
  - produces *receptive uterus* by **increasing the adhesiveness** of endometrial epithelial cells; by *increasing adhesive proteins* (**ICAM-1** and **VCAM-1**) and decreasing anti-adhesive proteins (mucin 1). This formation of tight junctions and receptive uterus pre**vents migration of the embryo outside the uterus** and helps it **continue developing**.
- The responsibility of corpus luteum to secrete hormones decreases as trophoblast is formed and contributes to the secretion of steroid hormones and placenta formation.

- The fetus (**fetal adrenal gland)** is responsible for **producing androgens** that will later on be **converted to estradiol** *inside the syncytiotrophoblast* by the action of **17 B HSD enzyme**.
- There is also **cortisol formation in the fetus**. The syncytiotrophoblast converts that *cortisol into dormant form (cortisone*) using the action of **11 B HSD Type 2**. This **protects the fetal adrenal axis from the maternal cortisol**.
- *The cortisol needs to leave the fetus by the third trimester.* ***Why****?* Because this ***marks and ends the pregnancy.*** It *initiates the delivery* by **starting the contractions**. It also helps to **lower the level of progesterone** as we near the end of pregnancy since we need The estrogen to initiate Uterine contractions.



3. Secretion of HCG and "rescue" of the corpus luteum

- The **trophoblast**, which will become the placenta, begins **secreting human chorionic gonadotropin (HCG**) approximately **8 days after ovulation**.
- HCG, which has biologic activity similar to LH, is critical because it "*informs" the corpus luteum that fertilization has occurred*.
- The **corpus luteum** (now under the direction of HCG) co**ntinues to synthesize progesterone and estrogen**, which *maintain the endometrium for implantation.*
- HCG from the trophoblast (placenta) "rescues" the corpus luteum from regression. (**Without fertilization** and the stimulation by HCG, the c**orpus luteum regresses 12 days after ovulation**, at which point it stops producing steroid hormones, and **menses occurs)**
- *The high levels of estrogen and progesterone* also **suppress** the development of the **next cohort of ovarian follicles.**
- Production of HCG ***increases dramatically during the first weeks*** of pregnancy. The ***pregnancy test*** is based on the excretion of large amounts **of HCG in urine**, which are measurable (beta subunit of the HCG hormone.). H**CG is detectable in maternal urine 9 days after ovulation**, even before the next expected menses


blastocyst
trophoectoderm
Inner cell mass
Early signaling:
LIF EGF
IL-1
trophoectoderm integrins
Local depletion of MUC1
microvilli
Regulation of immune tolerance integrin expression
Prostagladin and LIF production
pinopodes
Integrin profile of receptive endometrium
Progesterone stimulation of endometrium and decidualization of stroma
Endometrial glands
Endometrial capillaries

Hormones of pregnancy

- The duration of pregnancy is counted from the date of the last menstrual period.
- Pregnancy lasts approximately **40 weeks from the onset of the last menstrual period**, or **38 weeks from the date of the last ovulation.**
- Pregnancy is divided into **three trimesters**, each of which corresponds to approximately **13 weeks**.
- Hormone levels during pregnancy are depicted in Figure 10.11.
- First trimester:
  - HCG is produced by the **trophoblast,** beginning about 8 days after fertilization.
  - HCG "rescues" the corpus luteum from regression and, with an LH-like action , Stimulates corpus luteal production of progesterone and estrogen.
  - HCG levels are maximal at approximately gestational week 9 and then decline. Although HCG continues to be produced for the duration of pregnancy, its function beyond the first trimester is unclear.

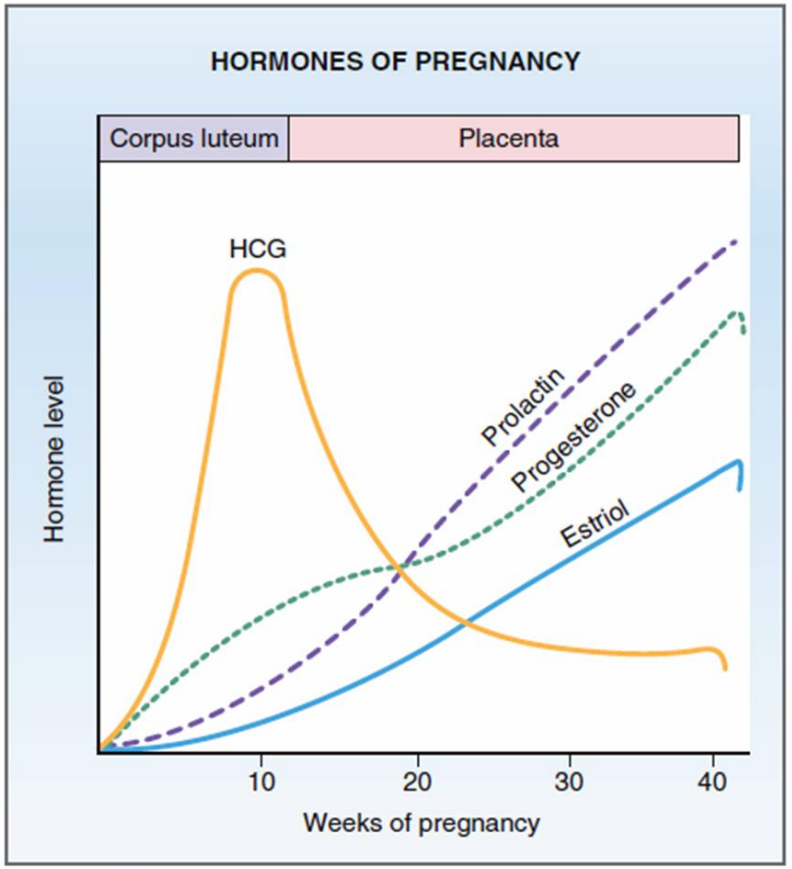
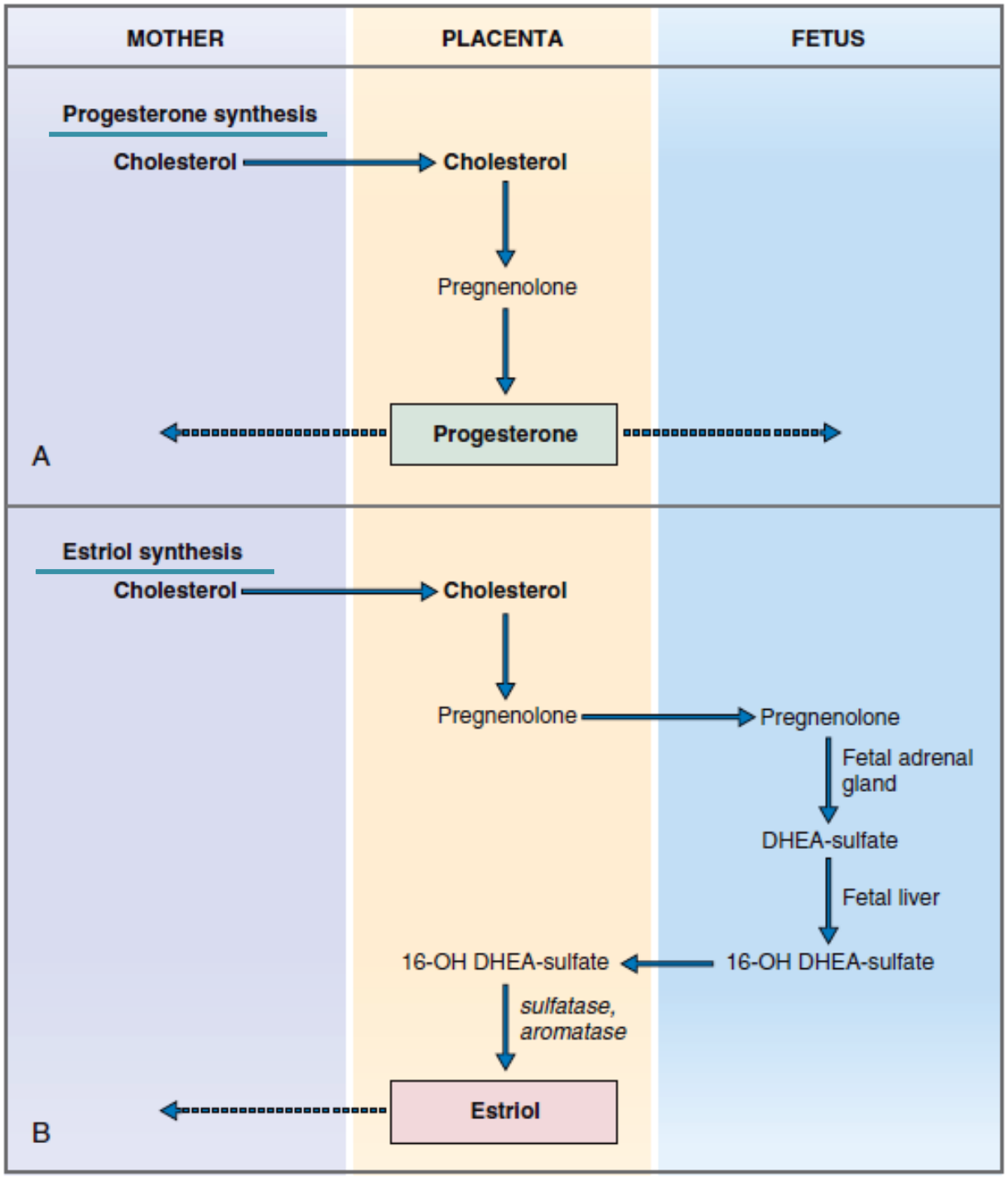


Fig. 10.11 Hormones of pregnancy. Number of weeks of pregnancy are counted from the onset of the last menses. *HCG,* Human chorionic gonadotropin.

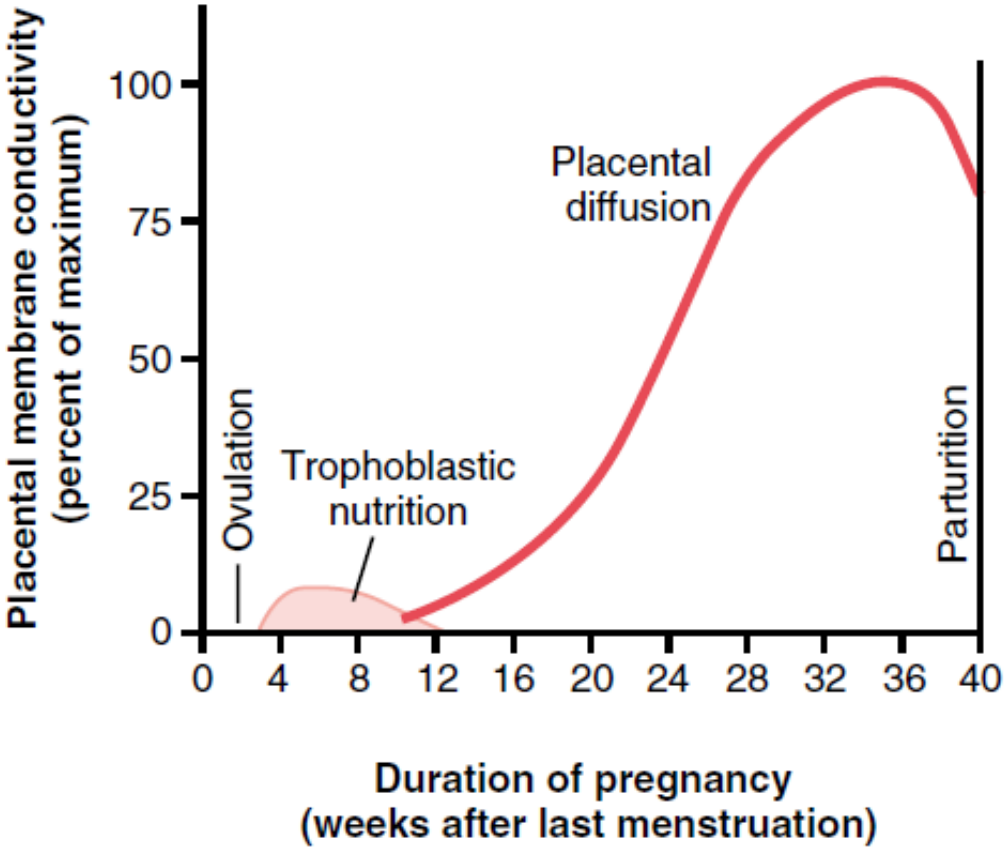
Hormones of pregnancy – Second and third trimester

- During the second and third trimesters, the placenta assumes responsibility for production of steroid hormones.
- **Progesterone** is produced by the placenta as follows: Cholesterol enters the placenta from the maternal circulation. In the placenta, cholesterol is converted to pregnenolone, which then is converted to progesterone.
- **Estriol,** the *major form of estrogen during pregnancy*, is produced through a coordinated interplay of the mother and the placenta, and, importantly, **requires the fetus.**
- Again, *cholesterol is supplied to the placenta from the maternal circulation* and is **converted to pregnenolone in the placenta**. *Pregnenolone then enters the fetal circulatio*n and is **converted to dehydroepiandrosterone-sulfate (DHEAsulfate)** in the **fetal adrenal cortex.** DHEA-sulfate is **hydroxylated** to **16-OH DHEA-sulfate** in the **fetal liver.** 16-OH DHEA-sulfate then **crosses back to the placenta**, where a **sulfatase** enzyme removes sulfate and **aromatase** converts it to estriol.
- The placenta also produces the peptide hormone **human placental lactogen** (hPL), which is structurally related to growth hormone and prolactin. hPL helps to **coordinate fuel economy** in the fetoplacental unit via *conversion of glucose to fatty acids and ketones*



Synthesis of progesterone (A) and estriol (B) during pregnancy. Progesterone is synthesized entirely by the placenta. Estriol synthesis requires the placenta, the fetal adrenal gland, and the fetal liver. (DHEA = Dehydroepiandrosterone).

Nutrition of the fetus



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.