

# L7-Physiology of pregnancy

Reproductive physiology



# Objectives

- Describe Fertilization & implantation of the blastocyst into the endometrium.
- Recognize the development and normal physiology of the placenta
- Describe the physiological functions of placental **hormones** during pregnancy
- Explain the physiological responses of mother's body to pregnancy



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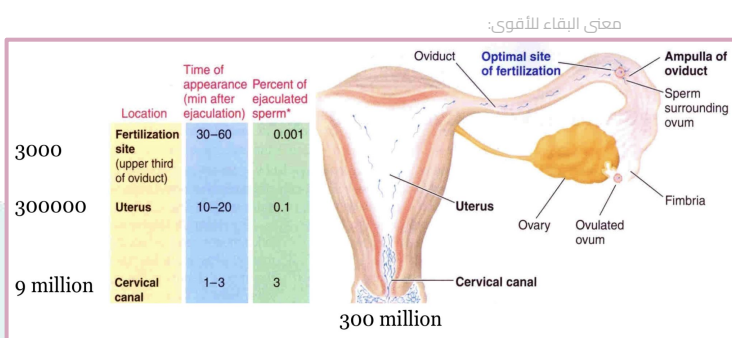
﴿ ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا  
الْعِظَامَ لَحْمًا ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ (14) ﴾

{ ثُمَّ خَلَقْنَا النُّطْفَةَ { التي قد استقرت قبل { علقة } أي: دما أحمر، بعد مضي أربعين يوما من النطفة، { فخلقنا العلقة } بعد أربعين يوما { مضغعة } أي: قطعة لحم صغيرة، بقدر ما يوضع من صغرها، { فخلقنا المضغعة } اللينة { عظاما } صلبة، قد تحللت اللحم، بحسب حاجة البدن إليها، { فكسونا العظام لحما } أي: جعلنا اللحم، كسوة للعظام، كما جعلنا العظام، عمادا للحم، وذلك في الأربعين الثالثة، { ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ } نفخ فيه الروح، فانتقل من كونه جمادا، إلى أن صار حيوانا، { فَتَبَارَكَ اللَّهُ } أي: تعالی وتعاظم وكثر خبره { أَحْسَنُ الْخَالِقِينَ } { الذي أحسن كل شيء خلقه وبدأ خلق الإنسان من طين ثم جعل نسله من سلالة من ماء مهين ثم سواه ونفخ فيه من روحه وجعل لكم السمع والأبصار والأفئدة قليلا ما تشكرون } فخلقته كله حيا، والإنسان من أحسن مخلوقاته، بل هو أحسنها على الإطلاق، كما قال تعالى: { لَنُدْ خَلْقْنَا الْإِنْسَانَ فِي أَحْسَنُ تَقْوِيمٍ } ولهذا كان خواصه أفضل المخلوقات وأكملها.

[تفسير السعدي]

# Introduction

- ◆ **How many sperms in the ejaculated semen?** 35-200 million sperms per ml of semen, usually 2-5 ml of semen is ejaculated. On average, half a billion sperms are deposited in the vagina, and only few thousands make it to the fallopian tubes. (Check pic1)
- ◆ **In which stage the ova is after ovulation?** Secondary oocyte, arrested at metaphase of meiosis II.
- ◆ **What is the % of ovulated ova that can reach fallopian tube?** Around 98%.
- ◆ **Can the ova that is released from the right ovary reaches the left fallopian tube?** Yes. some women who only had one ovary and only one remaining fallopian tube (on the contralateral side) had several children with ease. Ova are released into the abdominal cavity and are then picked up by the fimbriae of the fallopian tube which are equipped with cilia that beat inwards towards the uterus thereby reinforcing this "hooking" process.
- ◆ **What are the factors that help the ovulated ova to reach the fallopian tube?** 1- The cilia of the fallopian tubes beat towards the uterus. 2- Fluid. 3- Muscles lining the fallopian tube.
- ◆ **Is there any obstacles?** Yes, the irregularity of fallopian tube lining impedes the movements of the fertilized ovum, and the isthmus remain tonically constricted until progesterone causes its relaxation around three days after ovulation.
- ◆ **What are the factors that help the sperm to travel in the female genital tract?** Sperm motility through its flagella, PGs from the semen and oxytocin released from the female during orgasm can initiate antiperistaltic contractions that help propel sperm into the ovum, oocytes release certain chemicals that attract sperm through olfactory receptors and other factors.
- ◆ **Is there any obstacles?** Acidity of vaginal fluids, thick cervical mucus, possible antigenicity due to the occasional WBC infiltration of vagina and cervix, the barriers around ovum itself (zona pellucida and corona radiata)
- ◆ **How does the ova survive in the fallopian tube?** Secretion of peg cells of the fallopian tubes nourishes the ovum, the ovum is also protected by thick outer layer of glycoproteins (zona pellucida) and granulosa cells (corona radiata).



**TABLE 10.4** 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

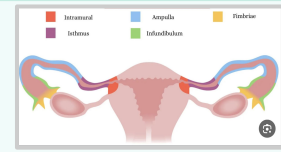
HCG, Human chorionic gonadotropin.

# Fertilization

الFertilization هو الإخصاب وهو إرتباط ال Male gamets مع ال Female gametes لتكوين ال Fertilized ovum وتسمى أيضا Zygote

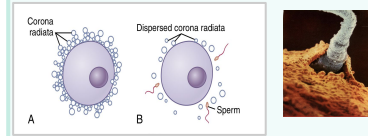
If the **ovum** becomes fertilized by a **sperm**, a new sequence of events called **gestation** or **pregnancy** takes place, and the **fertilized ovum** eventually develops into a full-term **fetus**.

» After ejaculation, sperms reach **ampulla of fallopian tube (site of fertilization)** within 30-60 min (Uterine contraction) check pic1, (aided by **contraction** of uterus and fallopian tubes, Prostaglandins & **oxytocin**). [1] (**Suction of sperms**)



» Sperm penetrate corona radiata and **zona pellucida** (hyaluronidase & proteolytic enzymes).

طبعاً لما السرم يدخل، البويضة تنقسم أحر المقسام (هالشيء ففما يصير اذا فيه حيوان منوي) لما تنقسم تعطي 2nd polar body  
ويصير اسم النواة حقتما Female pronucleus  
ونفس الشيء صار للحيوان المنوي، لما دخل انتفخ راسه عشان يسوي ال Male Pronucleus

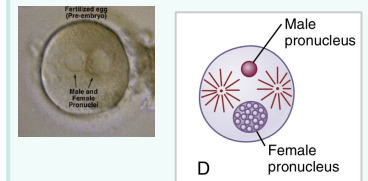


» Oocyte divides to form mature ovum (female pronucleus **23 unpaired chromosomes + 2nd polar body**).

طبعاً لما السرم يدخل، البويضة تنقسم أحر المقسام (هالشيء ففما يصير اذا فيه حيوان منوي) لما تنقسم تعطي 2nd polar body  
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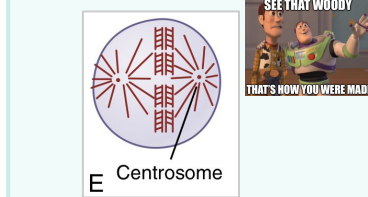
» Head of sperm swells (male pronucleus **23 unpaired chromosomes**).

ونفس الشيء صار للحيوان المنوي، لما دخل انتفخ راسه عشان يسوي ال Male Pronucleus



» Fertilized ovum (zygote) contains **23 pairs of chromosomes**.

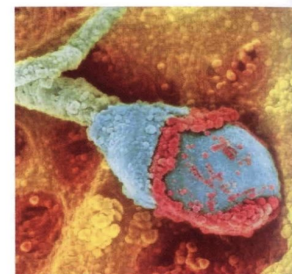
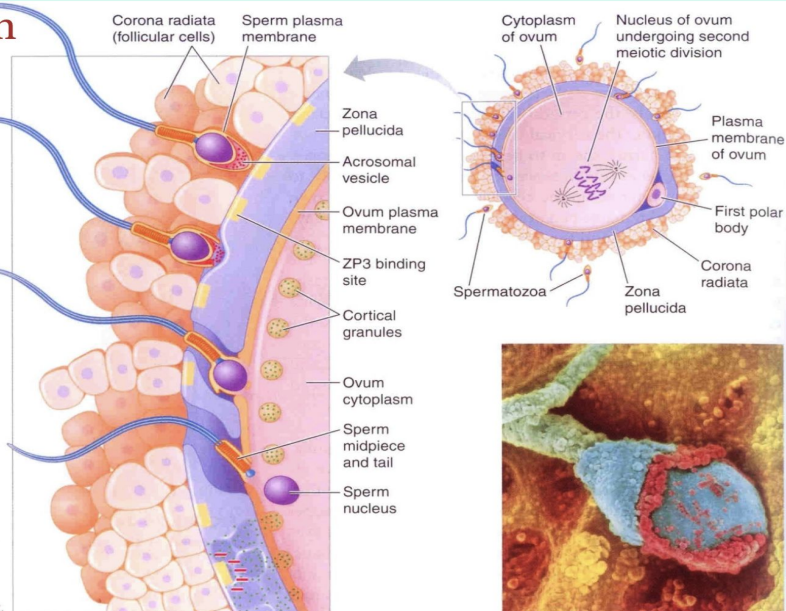
» The 23 chromosomes of the male and female pronuclei align themselves to re-form a complete complement of **46 chromosomes (2n)**



## Fertilization

- 1 The fertilizing sperm penetrates the corona radiata via membrane-bound enzymes in the plasma membrane of its head and binds to ZP3 receptors on the zona pellucida.
- 2 Binding of sperm to these receptors triggers the acrosome reaction, in which hydrolytic enzymes in the acrosome are released onto the zona pellucida.
- 3 The acrosomal enzymes digest the zona pellucida, creating a pathway to the plasma membrane of the ovum. When the sperm reaches the ovum, the plasma membranes of the two cells fuse.
- 4 The sperm nucleus enters the ovum cytoplasm.
- 5 The sperm stimulates release of  $Ca^{2+}$  stored in cortical granules in the ovum, which in turn, inactivates ZP3 receptors, leading to the block to polyspermy.

(a) Sperm tunneling through the barriers surrounding an ovum



(b) Scanning electron micrograph of spermatozoon with acrosomal enzymes (in red) exposed after acrosomal reaction

● FIGURE 20-25 Process of fertilization.

1: This transport of the sperm is aided by contractions of the uterus and fallopian tubes stimulated by prostaglandins in the male seminal fluid and also by oxytocin released from the posterior pituitary gland of the female during her orgasm. #Gyuton

2: Before a sperm can fertilize the ovum, it must dissolve these granulosa cell layers, and then it must penetrate through the zona pellucida, the thick covering of the ovum. To achieve this penetration, the stored enzymes in the acrosome begin to be released. The hyaluronidase among these enzymes is especially important in opening pathways between the granulosa cells so that the sperm can reach the ovum. #Gyuton

# Cleavage الانقسام

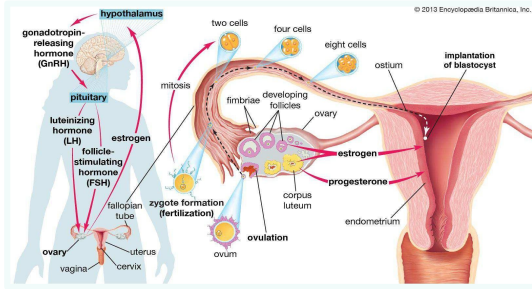
بعد الإخصاب تزل البويضة المخصبة للرحم بعد 3 إلى 5 أيام تقريباً، ما تزل بسرعة ليو؟ عشان يفتديها تنقسم عدة إنقسامات.

» Following fertilization, the zygote undergoes several **mitotic** divisions inside the zona pellucida (overall size does not change).

» First cleavage yields a 2 celled embryo, each cell is called: a **blastomere** and is **totipotent**.

» Divisions continue rapidly until the 32 cell stage (morula).

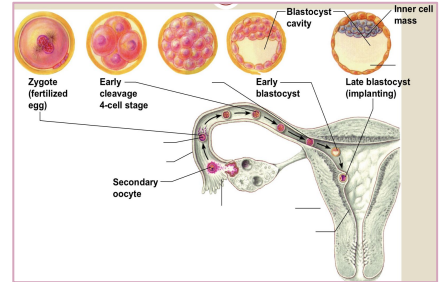
\* هنا Blastomere وليس Blastocyst، لأن البويضة فيها أكثر من بوية خلية، والتي تتكون بعد ثلاث أيام من الإخصاب، وهي Morula أصلاً لكن فيها سائل.



First cleavage → 2 cells "Blastomere"  
 Second cleavage → 4 cells  
 Third cleavage → 8 cells  
 Fourth cleavage → 16 cells "Morula"  
 Fifth cleavage → 32 cells "Morula"

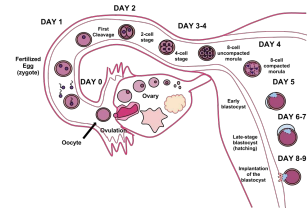


الفرق بين Blastomere و Morula ؟  
 Blastomere معناها خلية جنينية أولية)  
 أما Morula مأخوذة من Mulberry (التوت)  
 لأنها مرت بعدة إنقسامات 32 وحتى 16 ممكن  
 تسمى Morula.



## Transport of Fertilized Ovum and Implantation (Traveling)

» Zygote begins to divide as it travels through oviduct. The zygote **reaches** the **uterine cavity 3-5 days** after fertilization.

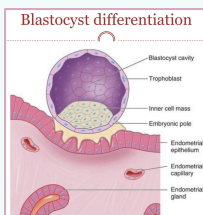
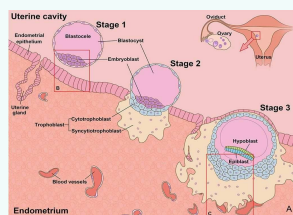
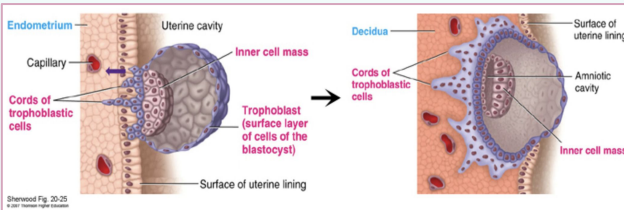


### Transport of Zygote in fallopian tube:

- » Mainly by Fluid current + Action of cilia + Weak contractions of the fallopian tube. (estrogen, PGs)
- » Delayed transport allows cell division to occur before the dividing ovum enters the uterus.
- » Isthmus (last two centimeters) spastically contracted first 3 days after ovulation, At this time increasing progesterone from corpus luteum → relaxes under effect of progesterone.
- » Blastocyst ~100 cells, enters the uterus. Implants into lining of uterus. Nutrition of blastocysts (secretory cells in fallopian tubes)

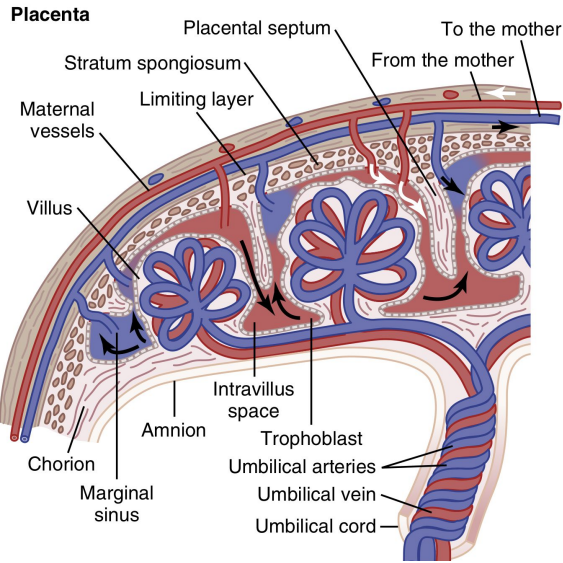
### Implantation:

- » Implantation occurs 5-7 days after Fertilization.
- » Digestion of endometrium
- » Decidual cells (glycogen, proteins, lipids & minerals)



# Physiologic Anatomy of placenta

EXTRA



الـ Trophoblastic cords التي طلعت من الـ Blastocyte الآن هي ماسكة بالرحم، هنا تبدأ أوعية دموية بالنمو داخلها، من وين جت؟ من الجنين الي قاعد ينمو، بعد ٢٠ يوم تقريبا يبدأ قلب الجنين يضخ الدم بهالوقت تبدأ تتكون blood sinuses من الأم، طبعاً Trophoblast cells تطوع projection أكثر ويصير اسمها placental villi (يصر فيها دم الجنين وحولها sinus أو مثل الجيب الي فيه دم الأم).  
دم الجنين يمشي كالتالي:

Two umbilical arteries → capillaries of the villi → back to fetus (single umbilical vein).

دم الأم بيكون:  
Uterine arteries → large maternal sinuses (surround villi) → back to uterine vein.

## Functions of placenta Overview

Respiration

Nutrition

Excretion

Endocrine

Protection

★ Trophoblastic cords from blastocyst.

★ Blood capillaries grow in the cords.

★ 21 days after fertilization, blood starts to be pumped by fetal heart into the capillaries.

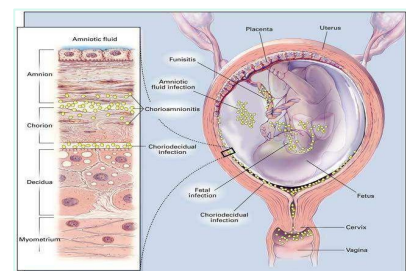
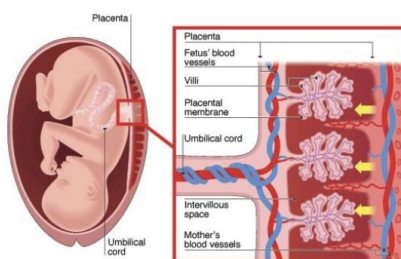
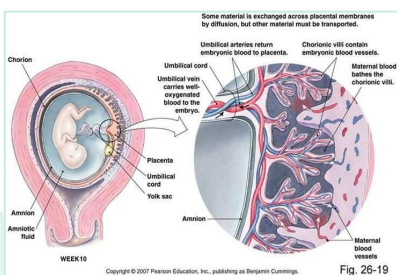
★ Maternal blood sinuses develop around the trophoblastic cords.

★ More and more trophoblast projections develop (placental villi).

مين يتنفس أول؟ مين ياخذ الأوكسجين أولًا ويستفيد منه الأم ولا الجنين؟  
الجنين.  
في الـ Pregnancy معلى الجنين أولًا (الجنة تحت أقدام الأمهات).

What are the Placental Hormones?

دا سؤال مهم



# Placenta Permeability and Membrane Diffusion Conductance

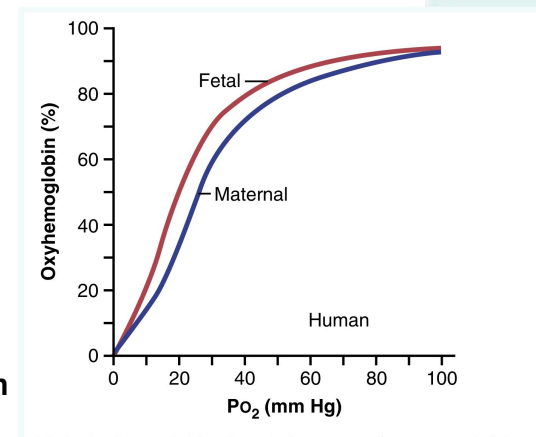
In Early pregnancy	the placental membrane is still thick and the surface area is small because it is not fully developed and grown. <b>Low Permeability</b>
In Late pregnancy	the permeability increases because of <b>thinning</b> of the <b>membrane</b> diffusion layers and because the <b>surface area expands</b> many times over. <b>Higher permeability</b> → increase placental diffusion

## Important Factor Facilitating Delivery of Oxygen to the Fetal Tissue (Respiration)

<p><b>Diffusion of Oxygen through the placental membrane:</b>*</p> <p><small>نفس تبدأ الالتهوية في الرئة أو تحدثون الرئيا « محدد بتذكر Don't stress</small></p>	<p><b>There are <u>three reasons why this low PO<sub>2</sub> is sufficient to deliver O<sub>2</sub> to the fetal tissues:</u></b></p>	<p><b>Hemoglobin of the fetus</b></p>
<p>» Dissolved O<sub>2</sub> in mother's blood (maternal sinuses) passes to fetal blood by <b>simple diffusion</b>.</p> <p>» The mean partial pressure of oxygen (PO<sub>2</sub>) of the mother's blood in the placental sinuses is about <b>50 mm Hg</b>, and the mean PO<sub>2</sub> in the fetal blood after it becomes oxygenated in the placenta is about <b>30 mm Hg</b>.  <b>50 mm Hg (M) – 30 mm Hg (F) = 20 mm Hg (mean pressure gradient).</b></p>	<p>1» <b>Hemoglobin of the fetus.</b></p> <p>2» High fetal hemoglobin concentration (<b>16-17 g/dl</b>) and it's about <b>50% greater</b> than that of mother Hb.</p> <p>3» <b>The Bohr Effect (وصف Affinity)</b>          مشروح بالسلايد التي بعد هذا وسبق أخذناه ، يقول Bohr: الهموقلوبين يقدر يتقبل اكسجين أكثر لما يكون PCO<sub>2</sub> قليل والعكس صحيح. دم الجنين الذي داخل للبلاستيتا شابلن كمية كبيرة من Co2 ولكن معظمه يروح لدم الام. الاذن صار دم الجنين more Alkaline بينما دم الام صار Acidic طيب وبعدين؟ هذا يؤدي الى ان دم الجنين يقدر يمسك O2 أكثر وبالتالي يقلل ان O2 يروح مع دم الام ويضمن ان الجنين ياخذ الO2. طيب وبتش Double Bohr effect شقوفا الصورة.</p> <div data-bbox="790 1512 941 1691"> </div>	<p>» Fetal hemoglobin (HbF) concentration is about <b>50% greater</b> than that of the mother (HbA). At low PO<sub>2</sub> HbF carry 20-50% more O<sub>2</sub> than HbA (HbF has a higher oxygen carrying capacity than HbA).  <b>HbF = Fetus = Affinity ↑</b></p>
<p><b>Other Factors</b></p> <ul style="list-style-type: none"> <li>• High maternal intervillous blood flow (almost double the fetal placental flow).</li> <li>• Increase pregnant temperature → shift to right.</li> <li>• High fetal cardiac output (120-170 BPM).</li> <li>• The fetal metabolic acidosis-which shifts the curve to the right and thus aids delivery of oxygen to the tissues</li> </ul>		

## Double Bohr effect

- 1 The maternal blood gains  $\text{CO}_2$ , the pH falls and the curve shifts to the **right** releasing additional oxygen.
- 2 On the fetal side of the placenta  $\text{CO}_2$  is lost, the pH rises and the curve shifts to the **left** allowing additional oxygen uptake.
- 3 (These changes cause the capacity of fetal blood to combine with  $\text{O}_2$  to increase, and maternal blood to decrease, which forces more  $\text{O}_2$  from the maternal blood while enhancing oxygen uptake by the fetal blood)\*.



## Nutrition

Fatty acids diffuse due to high solubility in cell membrane (more slowly than glucose).

$\text{K}^+$ ,  $\text{Na}^+$  and  $\text{Cl}^-$  diffuse with relative ease from maternal to fetal blood.

Fetus uses mainly glucose for nutrition so the trophoblast cells in placental villi transport glucose by carrier molecules; GLUT-1 (**facilitated diffusion**). GLUT-3 **Male doctor**

The placenta actively transports all amino acids, with fetal concentrations exceeding maternal levels.

## Excretion



1

Excretory products of the fetus diffuse through the placental membrane to maternal blood to be excreted with the waste products of the mother: Urea, uric acid and creatinine.

2

Higher conc. of excretory products in fetal blood ensures continuous diffusion of these substances to the maternal blood.



# Placenta as Endocrine Organ

أهم جزء بالمحاضرة:

	Characteristics	Functions
<b>Estrogen</b>	<ul style="list-style-type: none"> <li>» Steroid hormone.</li> <li>» Secreted by <b>syncytial trophoblast</b> cells.</li> <li>» Towards the end of pregnancy it reaches 30×.</li> <li>» Derived from weak androgen (<b>DHEA</b>) من وين؟ من Adrenal gland حقت الأم وحقت الجنين.</li> <li>» released from maternal &amp; fetal adrenal cortex.</li> </ul>	<ul style="list-style-type: none"> <li>» Enlargement of uterus, breast &amp; external genitalia.</li> <li>» Relaxation of pelvic ligaments in preparation for labor.</li> <li>» Activation of the uterus (gap junctions)</li> <li>» Increases blood volume of pregnant woman.</li> </ul> <p>It increases at the end also to prepare for labour, to terminate pregnancy.</p>
<b>Progesterone</b>	<ul style="list-style-type: none"> <li>» Steroid hormone.</li> <li>» Secreted by <b>syncytial trophoblast</b> cells.</li> <li>» Towards the end of pregnancy it reaches 10×.</li> <li>» Derived from cholesterol.</li> </ul>	<ul style="list-style-type: none"> <li>» Provides nutrition to developing embryo (<b>uterine secretory phase</b>).</li> <li>» Development of decidual cells <small>تغذي الجنين</small>.</li> <li>» Inhibits the contractility of the uterus.</li> <li>» <b>Development of breast lobules and alveoli.</b></li> <li>» Increases the sensitivity of respiratory center to CO<sub>2</sub></li> </ul>
<b>Relaxin</b>	<ul style="list-style-type: none"> <li>• Polypeptide.</li> <li>• Secreted by corpus luteum and placenta.</li> </ul>	<ol style="list-style-type: none"> <li>I. Relaxation of symphysis pubic ligament (weak).</li> <li>I. Softens the cervix at delivery. <small>ليه ضعيف؟ لان هذا دور الاستروجين اصلا</small></li> </ol>
<b>Human Chorionic Gonadotropin (hCG)</b>	<ul style="list-style-type: none"> <li>» Glycoprotein.</li> <li>» Secreted by: <b>syncytial trophoblast cells</b>, shortly after blastocyst implant!</li> <li>» <b>Used for pregnancy test.</b></li> </ul> <p>Appears in blood 8-9 days after fertilization, while in urine it appears <b>2-3 weeks</b> after fertilization IMP MCQ</p>	<ul style="list-style-type: none"> <li>» <b>Most important function is to maintain corpus luteum (↑estrogen &amp; progesterone) till 13-17 weeks of gestation.</b></li> <li>» Exerts interstitial (Leyding) cell-stimulating effect on testes of the male fetus (growth of male sex organs).</li> <li>» TSH-like activity to increase thyroxine production (in mother).</li> </ul>
<b>Human Chorionic (Somatomammotropin) or Human Placental Lactogen (hPL)</b>	<ul style="list-style-type: none"> <li>» Protein hormone.</li> <li>» Secreted by <b>placenta</b> around 5<sup>th</sup> gestational week.</li> </ul>	<ul style="list-style-type: none"> <li>» <b>Breast development. (hPL facilitates mammogenesis)</b></li> <li>» Weak growth hormone's action.</li> <li>» <b>Inhibits insulin sensitivity</b> = ↓ glucose utilization. (gestational diabetes)</li> <li>» Promotes release of fatty acids from fat stores of mother → alternative source of energy for mother.</li> </ul>

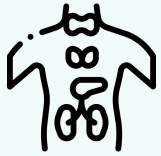
عشان تدخل البويضة المخصبة أو الـ Zygote للرحم، لازم "نسبة الإستروجين لا بروجستيرون قليلة" وهنا يجي دور الـ Corpus luteum لأنه يفرز كمية كبيرة من البروجستيرون، لذلك بداية الحمل يكون مرتفع.

بعد عملية الـ implantation وتكون الـ Trophoblast تبدأ هذه الخلايا تفرز HCG وهو هرمون مشابه وظيفيا للـ LH، يروح للـ corpus luteum ويقول انه حصل اخصاب (عشان يحافظ عليه لأن لو ما وصلت له هالإنشارة يبصير له regression وتبدأ الدورة) وأيضاً يحفز انه يزيد إفراز البروجستيرون والإستروجين.



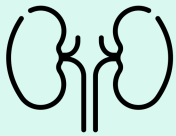
Extra (Hormones of pregnancy) Graph, your Finger [HERE](#) please!

# Physiological Adaptation to Pregnancy



## Maternal Endocrine System

- Anterior pituitary gland enlargement (50%):
  - Release of ACTH, **TSH and PL increase.**
  - FSH and LH almost totally suppressed.
- Adrenal gland:
  - Increase glucocorticoids secretion (mobilize AA).
  - Increase aldosterone (retain fluid)/(reabsorb excess Na).
- **Thyroid gland enlargement (50%):**
  - Increase thyroxine production (hCG). **Physiological goiter**
- Parathyroid gland enlargement:
  - Increase PTH secretion (maintains normal  $Ca^{+2}$ ).



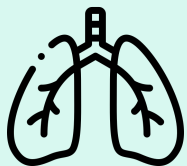
## Metabolism & Kidney Function

- Increase basal metabolic rate (15%).
- Increase in daily requirements for:
  - Iron.
  - Phosphates.
  - Calcium.
  - Vitamins: vitamin D ( $Ca^{+2}$  absorption).
- The renal tubules' reabsorptive capacity for Na, Cl, and water is increased as much as 50%.
- The renal blood flow and GFR increase up to 50%.
- Normal pregnant woman accumulates only about 5 pounds (2.27Kg) of extra water and salt.



## Circulatory System

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



## Respiration

- Increase in  $O_2$  consumption (20%):
  - Increase BMR.
  - Increase in body size.
- Growing uterus presses upwards (restriction)
- Increase in respiratory rate (RR).
- Progesterone ↑ sensitivity of respiratory centers to  $CO_2$ .
- Increase in minute ventilation ( **Tidal Volume x Respiratory Rate** ) by 50% **and a decrease in arterial  $PCO_2$  to several millimeters.**

## 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).
  - Increase appetite.
  - Removal of food by fetus.
  - Hormonal effect.

Before implantation, the blastocyst obtains its nutrition from the uterine endometrial secretions. How does the blastocyst obtain nutrition during the first week after implantation?

It continues to derive nutrition from endometrial secretions	The cells of the blastocyst contain stored nutrients that are metabolized for nutritional support	The placenta provides nutrition derived from maternal blood	The trophoblast cells digest the nutrient-rich endometrial cells and then absorb their contents for use by the blastocyst
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A 28-year-old woman develops nausea and breast tenderness after missing her menstrual period. A digital home pregnancy test is positive. Other than lower back pain, occasional headaches, and frequent urination, the pregnancy progresses to the second trimester without complications.  
1-With respect to hormonal changes during pregnancy, which of the following is the source of estrogen and progesterone during the first 2 months of pregnancy?

Anterior pituitary	Corpus luteum	Ovary	Placenta
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Using the case in previous question, Which of the following is the source of estrogen and progesterone during the last 7 months of pregnancy?

Anterior pituitary	Corpus luteum	Ovary	Placenta
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Want Explanation ? [Your Finger HERE!](#)

## Leaders

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Fahad Almughaiseeb



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(Very special Thanks for the ones who rated the last Lecture!!)

