

Oogenesis

Dear fellow colleagues, the embryology course you've been submitted to requires the slides that the doctor uploads as a material for the exam, these sheets are made for understanding the lectures and are not required in the exam, thank you.

A very important note:

*This chapter specifically depends on the differentiation between the different structures throughout the progress of producing the oocytes. So I have used this tip where I highlighted the **oocytes** stages with **pink** while the developments of the **follicular cells** with **grey**.*

What is oogenesis?

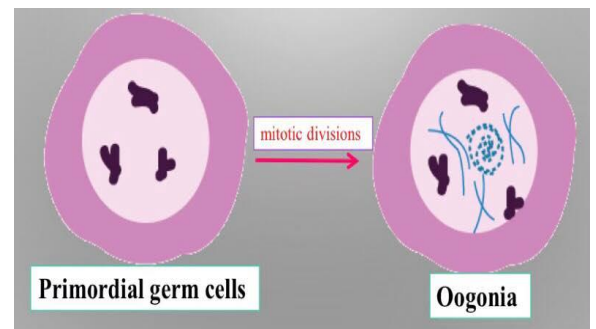
Oogenesis is the production of female gametes (**oocytes**) in the ovaries. It begins in the intra-uterine (inside the uterus) of a pregnant mother while the female is still an embryo in the womb (before birth) and continues after birth.

Let's move on to the progress of oogenesis:

An embryo has a few cells at first created, for example, at one week old, the embryo contains less than 50 cells as whole and they multiple as the embryo grows older. Some of these cells migrate from the **epiblast** (the origin of all cells including the germ/sex cells) and move to the **wall of yolk sac** (which is similar to the yolk sac in the chicken eggs that is used for feeding the chicks but here it doesn't have the same function and it regresses).

During the fourth week till the end of fifth week, those cells which are called the **Primordial Germ Cells** begin to migrate from the yolk sac toward the developing gonads **ovaries**. Once they reach the ovaries, they start mitotic divisions to increase in number and get called **Oogonia**.

Oogonia = Primordial Germ Cells gone through mitotic divisions



The journey of the Primordial Germ Cells can be summarized as the following:

Epiblast (the origin of all cells) ➡ The Yolk Sac (there is not much about them staying here) ➡ Ovaries (the gonads of a female)

Oogonia reach the ovaries looking for **shelter**, so by the end of the third month, they become arranged in clusters and get surrounded by large flat epithelial cells called **follicular cells** to provide protection (note that all of them cluster and get surrounded by the follicular cells together, **not individually**). Since Oogonia are still limited in number, they continue mitotic divisions to increase. Some of them arrest in their cell divisions in prophase meiosis 1 and form primary oocyte.

By the end of the fifth month, oogonia reach **maximum** about 7 million to get through natural selection and further modifications to pick up the best ones.

By the end of the seventh month, the majority of oogonia become **atretic** and get *degenerated* due to the lack of blood supply and nutrients except for the ones that are at the surface of the ovaries near the blood supply.

All the surviving **primary oocytes** commit to *Meiosis I* and get into Prophase. They also get surrounded **individually** by a layer of flat cells (follicular epithelial cells).

***Primary oocyte** is the cell produced by the last stage of mitosis of oogonia and it commits to meiosis to produce the oocyte needed for fertilization.

Primordial Follicle = Primary oocyte surrounded by follicular cells

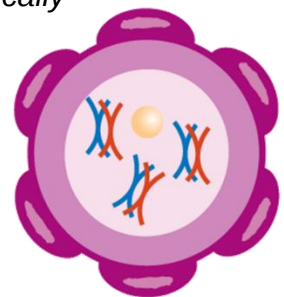
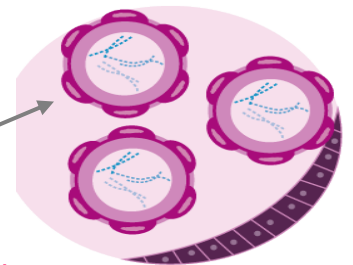
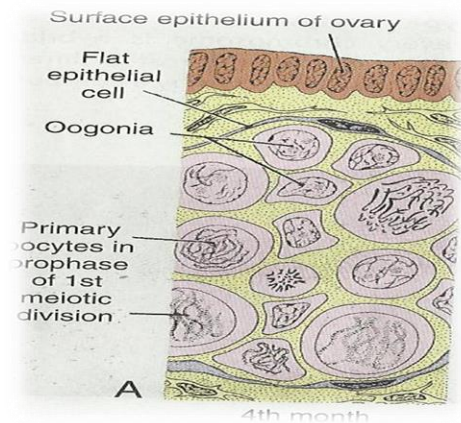
Near the time of birth, the follicles surrounding the Primary Oocytes in the Primordial Follicles produce a small peptide called the **Oocyte Maturation Inhibitor (OMI)** which freezes Meiosis I of the primary oocyte at the **diplotene** stage and prevents it from proceeding to Metaphase I and completing Meiosis I before puberty is reached (*that actually is considered as a blessing for the females because if Meiosis was completed, that means that the girl when born will be able to get pregnant right away and it surely doesn't make sense for a baby to get pregnant because basically she is not physically able to carry a baby since she is one*).

So, a female gets born with 600K-800K primordial follicles (primary oocytes surrounded by follicular cells arrested in diplotene stage of prophase in Meiosis I) inside her ovaries.

***The diplotene stage** is when the analogous double structured chromosomes are crossing over without being separated.

During childhood, most oocytes become atretic and only 40K remain till the beginning of puberty. Fewer than 500 get ovulated.

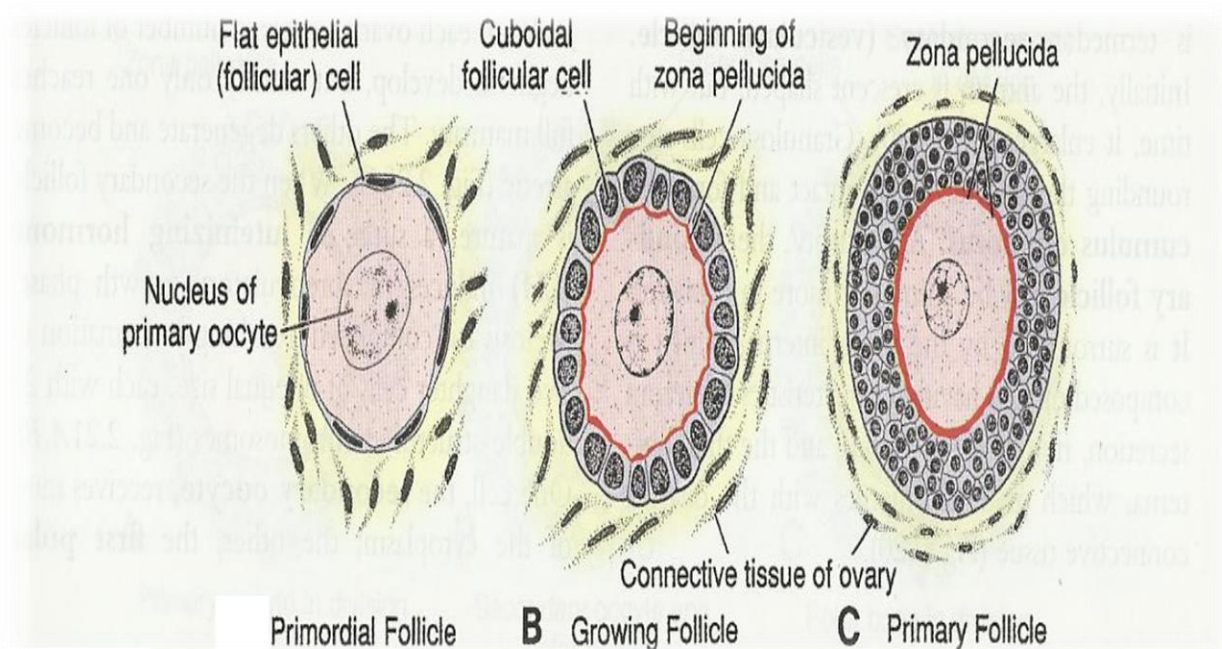
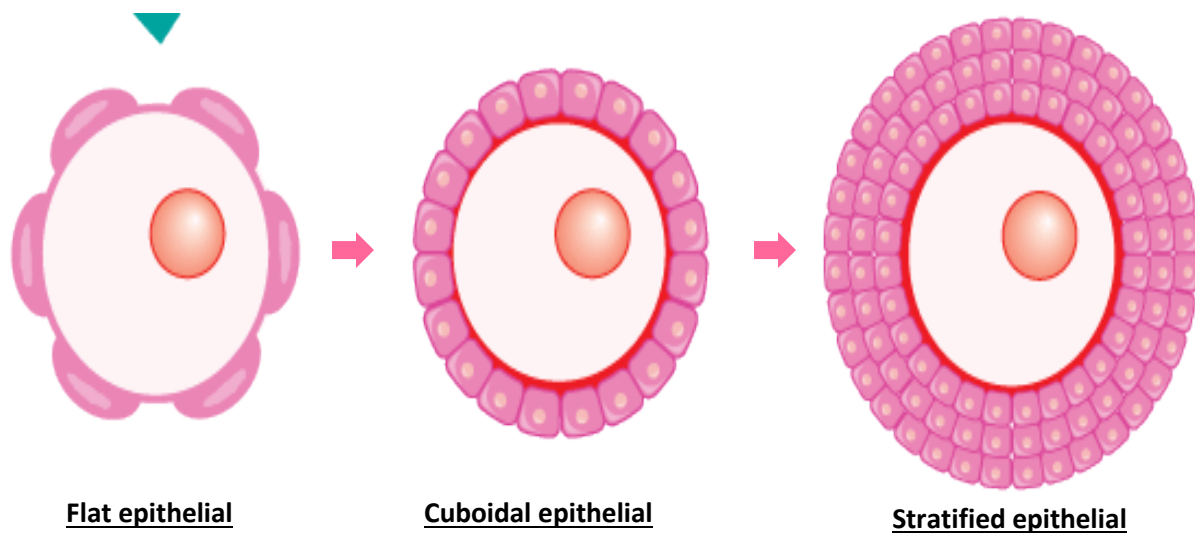
At puberty, the brain gives a command to the hypothalamus to secrete gender hormones that stimulate the **Pituitary Gland** to secrete the two hormones: **FSH** (follicle stimulating hormone) and **LH** (luteinizing hormone).



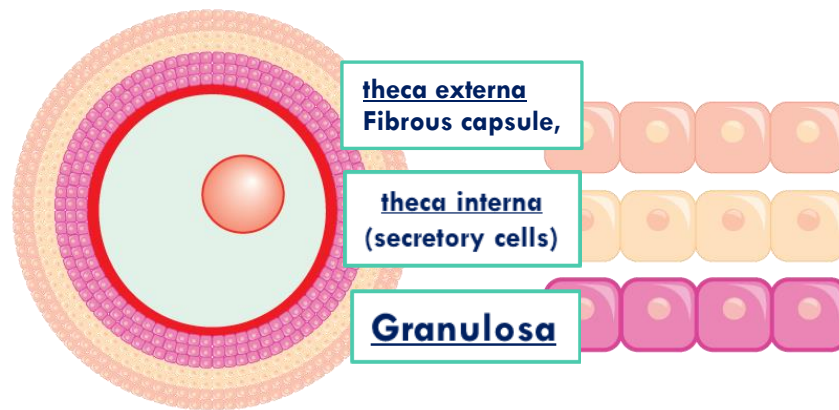
FSH provokes and evokes 15-20 of the **primordial follicles** the female has been born with and matures them by passing through 3 stages each month and only one of these follicles reaches full maturity. Only one mature oocyte gets ovulated each month by one of the two ovaries.

The first stage of follicular maturation: **Primordial follicle** → **Primary (preantral) follicle**

Firstly, **FSH** selects 15-20 of the primordial follicles to mature them. This maturation is basically about stimulating follicular (granulosa) cells around the oocyte through increasing the number of layers of follicles surrounding the primary oocyte alongside to creating the zona pellucida by the contribution of the primary oocyte and the follicular cells.



As the primary follicle continues to grow granulosa cells rest on a basement membrane separating them from surrounding ovarian connective tissue (stromal cells) that form the (theca folliculi).



Let's talk about the importance of zona pellucida which is a layer of glycoproteins on the surface of the oocyte secreted by the primary oocyte and follicular cells:

Zona Pellucida is the wall that facilitates the entrance of only one sperm. Remember, it's not a barrier, it prevents polyspermy (fertilization by more than one sperm) and facilitates the fertilization by one sperm only. In addition to that, the journey from the fallopian tube to the uterus is 4 days and zona pellucida prevents the implantation of the zygote in the fallopian tube throughout this period and gets it implanted in the uterus. So, if the pregnant woman had a defect in the zona pellucida, the zygote might get implanted in the fallopian tube and because this isn't the right state (the fallopian tube is so thin and doesn't fit for a whole embryo to grow in), this mostly leads to the death of the embryo and bleeding occurs, if the woman was not treated quickly, she might also die.

Theca externa is a fibrous capsule used for protection.

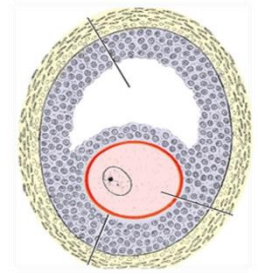
Theca interna and Granulosa cells produce a very important hormone called **Estrogen**, **Estrogen** is responsible for:

- Inducing the uterine endometrium
- Thinning the cervical mucus to ease the passage of the sperm
- Stimulating the anterior pituitary gland to secrete **LH**.

The second stage of follicular maturation: Primary follicle ➡ Secondary (antral) follicle

Granulosa cells and Theca Interna both secrete a fluid called antrum, in which fills the gaps between the Granulosa Cells. The moment antrum appears; the follicle is called **antral/vesicular/secondary follicle**.

Do notice the oocyte itself is still primary (it didn't divide or develop) only the follicles surrounding it are developing. In other words, the princess is still sleeping and everything around is changing.



The third stage of follicular maturation: Secondary follicle → Preovulatory follicle

When the secondary follicle is mature, a surge in luteinizing hormone (LH) promotes the Preovulatory growth phase.

LH wakes up the primary oocyte and tells it to finish its Meiosis I because in no time (about one day only) it is going to be ovulated.

Throughout the Preovulatory Growth Phase, three things happen:

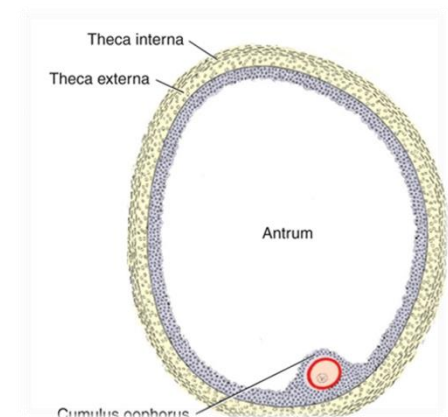
- The **primary oocyte** finishes *Meiosis I* by influence of LH and produces two daughter cells of (1n): the **first polar body** and the **secondary oocyte**. The **secondary oocyte** enters meiosis II and gets arrested in metaphase 3 hours before ovulation. The secondary oocyte is bigger than the first polar body so it steals its cytoplasm and usually the polar body dies due to lack of nutrients. If it stays alive, it proceeds to meiosis II and gets arrested in metaphase alongside the secondary oocyte until a sperm enters and induces them to finish Meiosis II.
- Antrum gets enlarged with time
- Granulosa cells surrounding the oocyte remain intact and form the **cumulus oophorus**

The resulting cell is called: **Preovulatory Follicle**.

What's a preovulatory (graafian) follicle?

A **Cumulus oophorus** consisting:

- 1-Granulosa cells
- 2-Zona pellucida
- 3-Secondary oocyte arrested in metaphase stage of meiosis II
- 4-First polar body



Throughout the time till Ovulation, LH secretion increases:

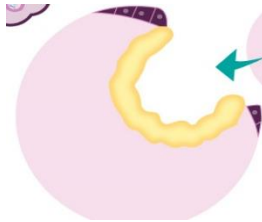
- The surface of ovary bulges locally
- Digestion of collagen around follicle
- Local muscular contraction in ovarian wall

All this will help in extrude the oocyte with surrounding granulosa cells that form (cumulus oophorus) BREAK FREE (ovulation) and float out of the ovary.

Some of (cumulus oophorus) rearrange themselves around zona pellucida to form (Corona Radiata). Corona Radiata and the secondary oocyte get ovulated at day 14 and carried into the fallopian tube by these sweeping movements of the fimbriae and by motion of cilia on the epithelial lining.

After ovulation, granulosa cells remaining in the wall of the ruptured follicle, together with cells from the theca interna, are vascularized by surrounding vessels. Under the influence of LH, these cells develop a yellowish pigment and change into lutein cells, which form the **corpus luteum** and secrete estrogens and progesterone.

Progesterone, together with some **estrogen**, causes the uterine mucosa to enter the progestational or secretory stage in preparation for implantation of the embryo.



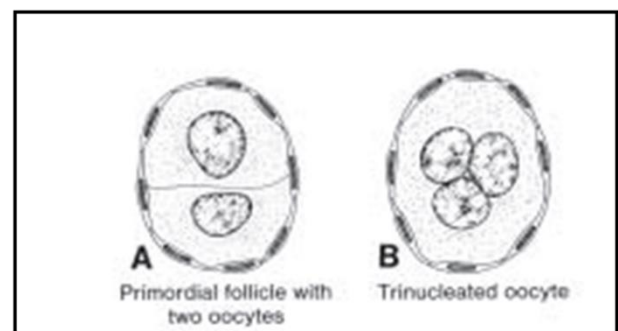
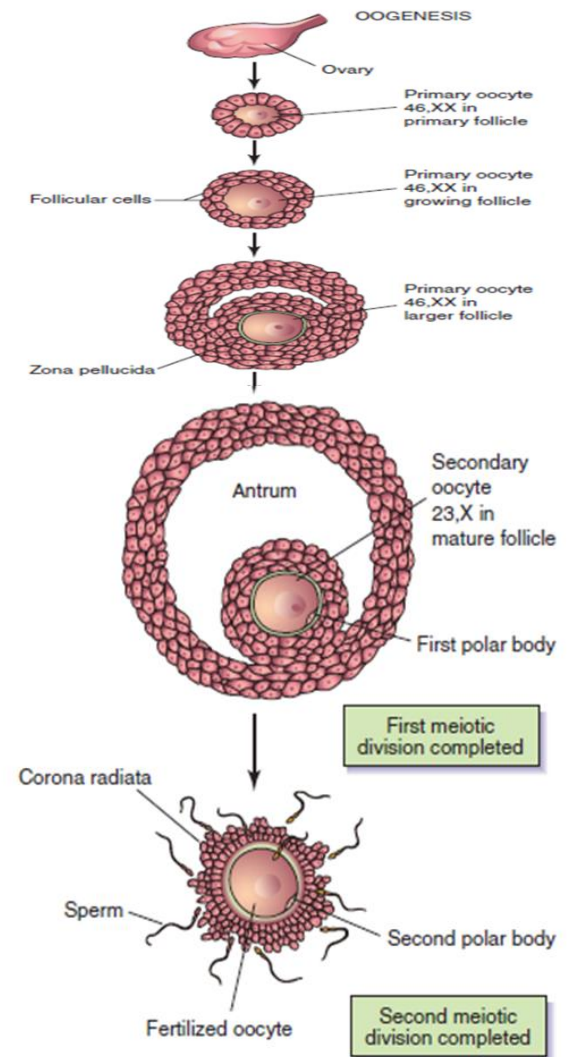
Fertilization:

- *If there is a sperm in the tube, the oocyte is fertilized and completes meiosis II, the sperm then continues the work a zygote is produced*
- *If there is no sperm, the oocyte is not fertilized and gets degenerated approximately 24 hours after the ovulation bleeding happens*

Abnormal Gametes:

- In humans, **one ovarian follicle** occasionally contains two or three clearly distinguishable primary oocytes

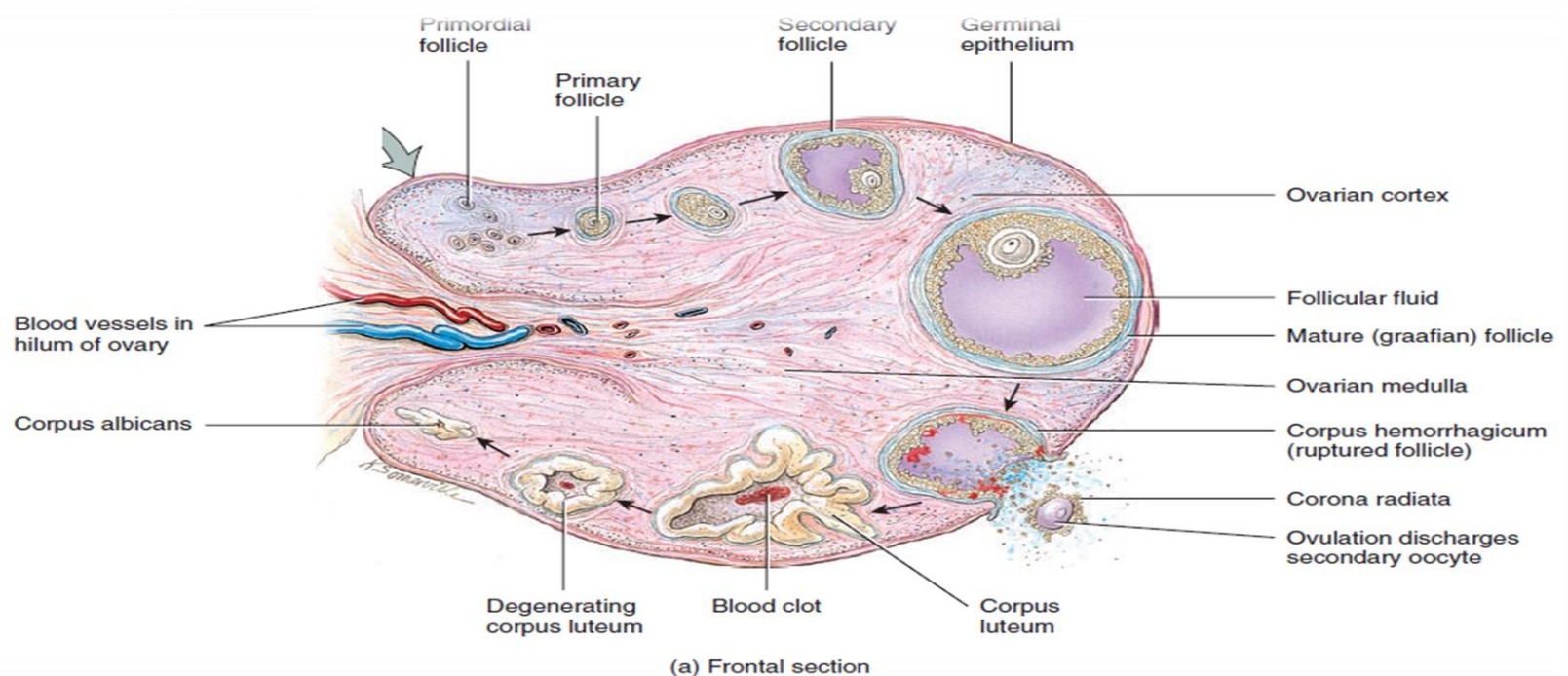
Although these oocytes may give rise to twins or triplets, they usually degenerate before reaching maturity.



- In rare cases, one primary oocyte contains two or even three nuclei. *Such binucleated or trinucleated oocytes die before reaching maturity.*

OOGENESIS

- Primordial germ cells arrive in the indifferent gonad at week 4 and differentiate into oogonia.
- Oogonia enter meiosis I to form **primary oocytes**. All primary oocytes are formed by **month 5 of fetal life** and are **arrested the first time in prophase (diplotene) of meiosis I** and remain arrested until puberty.
- Primary oocyte arrested in meiosis I are present at birth.
- When a girl reaches puberty, during each monthly cycle a primary oocyte becomes unarrested and completes meiosis I to form a secondary oocyte and polar body.
- The secondary oocyte becomes **arrested the second time in metaphase of meiosis II** and is ovulated.
- At fertilization within the uterine tube, the secondary oocyte completes meiosis II to form a **mature oocyte** and **polar body**.



Some conceptual notes:

- You may ask yourself why does the secondary oocyte steal the cytoplasm of the first polar body? Well, that's because the secondary oocyte is bigger and is the one that's going to get fertilized so it prepares itself for the fertilization because the sperm basically will have no food or mitochondria when it arrives to the oocyte.
- If one oocyte gets ovulated only, why does FSH mature 15-20 follicles? These follicles have a really important role in secreting Estrogen and Progesterone (the functions written upwards). That's why these follicles grow and through natural selection, the best oocyte gets ovulated.
- The main difference between the female and the male is mainly the fact that the woman takes pregnancy in addition to producing gametes while the male produces gametes only.
- The male can produce gametes starting from puberty till the moment he dies (although the fertility decreases with the increase of age) but the woman has got a finite productive life *approx. 35 years* (from age 15 till age 45~50), that's also because of the fact that she is the one who gets pregnant and only throughout this time, she is physically able to do that.
- A woman produces one oocyte from one of the two ovaries each month, she produces 10~12 oocytes in the year, about 250 oocytes are produced by each ovary throughout her life, yet she has 7 million oocytes at the beginning to get through natural selection and select the best out of the best.
- The only time a female has a haploid cell ($1n$) is the secondary oocyte.
- For females who aren't in a sexual interaction, they never complete Meiosis II.
- If the first polar body didn't die, it completes meiosis and produces 2 secondary bodies.
- If fertilization and the previous point happened, the final produced cells are: 3 secondary polar bodies and one fertilized egg.
- Because it may take too long for a female to get her puberty (secretion of LH) and the chromosomes stay undivided in the diplotene stage, some abnormalities when dividing may occur such as Monosomy and Trisomy.
- The gender of a baby can't be known until the outer genital parts develop.
- The follicles under FSH secrete Estrogen and under LH they secrete Progesterone.
- **EXTREMELY IMPORTANT: DO DIFFERENTIATE BETWEEN THE DIFFERENT STAGES OF OOCYTES AND FOLLICULAR CELLS AND KNOW THE DIFFERENCES IN STRUCTURE BETWEEN EACH OF THEM BECAUSE THE DOCTOR SAID IT'S A SURE QUESTION IN THE EXAM. GOOD LUCK!**

Done by: Zina Smadi

Corrected by: Sabina Khdairi & Abdulrahman Jabr