Lesson: Physiology of the ovary
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# Physiology of the ovary

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INTRODUCTION

The ovary (From Latin: ovarium, literally "egg" or "nut") is a gamete producing reproductive organ in females. Ovaries work as both female gonads and endocrine glands. Though the process of gamete formation in the ovary is initiated in female fetus, however the ovary starts functioning as an endocrine gland only after puberty.

The process of gamete formation in the ovary is termed as oogenesis, involves formation of an ovum from primordial germ cells through a number of morphological, genetic and physiological changes. These changes consist of oocyte maturation, cytoplasmic maturation and meiotic division. The primordial germ cells once at the genital ridge, differentiates into oogonia. These cells further divide exponentially to form huge pile of oogonial germ cells. A few of these oogonia develop into large cells called primary oocytes and are surrounded by a number of somatic cells; this structure is termed ovarian follicle. After onset of puberty, a number of primary oocytes are recruited to undergo maturation and meiotic division, eventually give rise to ovum.

Folliculogenesis is a sub-process involving maturation of ovarian follicle. It describes the progression of a number of small primordial follicles into large pre-ovulatory follicles.

During the process of ovulation, the ovum is released and if fertilized, forms a zygote. The left out follicle in the ovary undergo differentiation to form corpus luteum, the process is termed as Luteinization. Corpus luteum actively secretes hormone in anticipation of pregnancy and is maintained as such in the ovary throughout or for duration of pregnancy depending upon the species. However, in the absence of pregnancy the corpus luteum degenerates to corpus albicans, the process termed as Luteolysis.

The cyclic changes in the uterine epithelium collectively termed as menstrual cycle are the manifestations of endocrine release of steroid hormones synthesized in the ovary during the process of folliculogenesis. Thus, the process of folliculogenesis is tightly coordinated with the menstrual cycle. The follicular phase in ovary corresponds to the proliferative phase and the luteal phase corresponds to secretory phase of menstrual cycle.

All these process of oogenesis; folliculogenesis, ovulation and luteinization are tightly regulated by the endocrine secretions from pituitary. The trophic hormones released from the hypothalamus termed as Gonadotropin Releasing Hormones (GnRH) regulate the endocrine secretions of pituitary, which in turn releases two hormones, named as Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), regulating the secretions of ovary.

The endocrine secretions of ovary mainly consist of steroid hormones, estrogens and progesterone. These hormones are responsible for maintenance of reproductive organs and development of secondary sexual characters in the female. Moreover, these hormones also govern their own synthesis by feedback mechanism at the level of both pituitary and hypothalamus.

In this chapter sequential events of gamete formation are first described followed by a description of their regulation.
Physiology of the ovary

Morphology of the adult ovary

Ovaries are paired glands, in case of humans, they are oval shaped and whitish in colour and lie on either side of the uterus. Ovaries are located in a shallow depression called **ovarian fossa** one on either side in the lateral wall of the pelvic cavity. Ovary descends to the brim of the superior portion of the pelvic cavity during the third month of fetal development in humans and remains attached to the lateral pelvic wall. A series of ligaments holds them in position.

- The **BROAD LIGAMENT** of the uterus attaches to the ovaries by a double layered fold of peritoneum called the **MESOVARIUM**.
- The **OVARIAN LIGAMENT** anchors the ovaries to the uterus
- The **SUSPENSORY LIGAMENT** attaches ovaries to the pelvic wall.

Each ovary contains a **HILUM**, the point of entrance and exit for blood vessels and nerves along which the mesovarium is attached. (Fig. 1)

![Fig1. Location and attachments of an adult ovary](http://en.wikipedia.org/wiki/Adnexa_of_uterus#mediaviewer/File:Gray1161.png)

Physiology of the ovary

Histology of the ovary

Each ovary consists of the following parts:

*Germinal epithelium:* is a layer of simple epithelial (low cuboidal or squamose) that covers the surface of the ovary.

*Tunica albuginea:* is a whitish capsule of dense irregular connective tissue located immediately deep to the germinal epithelium. The germinal epithelium and tunica albuginea together form ovarian capsule. The layer deep to the tunica albuginea is termed *ovarian cortex.* It consists of ovarian follicles surrounded by a dense layer of connective tissue that contains collagen and fibroblast-like cells called *stromal cells.* The oocyte surrounded by a layer of differentiated stromal cells is termed as an ovarian follicle (or *primordial follicle*). These primordial follicles undergo a series of changes through primary, secondary, tertiary and *preovulatory follicle* to finally release the secondary oocyte. Following ovulation, the follicle becomes *corpus luteum* and in absence of pregnancy it degenerates to form *corpus albicans* and all these types of follicles are present in the cortical region of the ovary. (Fig. 2)

The *ovarian medulla* makes the central region of the ovary deep to the cortex. The border between cortex and medulla is indistinct, but the medulla contains more loosely arranged connective tissues, lymphatic vessels, blood vessels and nerves.

![Section of the ovary](image)

**Fig. 2. Section of the ovary.** 1. Germinal epithelium. 2. Central stroma. 3. Peripheral stroma. 4. Blood vessels. 5. Vesicular follicles in their earliest stage. 6, 7, 8. More advanced follicles. 9. An almost mature follicle. 9. Follicle from which the ovum has escaped. 10. Corpus luteum.
Oogenesis

The process of formation of gametes in ovary is termed as oogenesis. This process of gamete formation begins in ovary even before a female is born.

It occurs in the following sequence (Fig. 3)

- During early fetal development, the primordial (primitive) germ cells migrate from yolk sac epithelium to the ovaries.
- These germ cells differentiate into Oogonia within the ovaries.
- Oogonia are diploid stem cells which divide mitotically to produce millions of germ cells most of which degenerate*.
- However, a few of them develop into larger cells called Primary oocytes that enter prophase of meiosis I but do not complete that until after puberty. During this arrested stage of development, each primary oocyte is surrounded by a single layer of flat follicular cells, and the entire structure is termed as Primordial follicle.
- At puberty, a few primary oocytes complete meiosis I and produce a secondary oocyte and first polar body. The secondary oocyte has half the number of chromosomes (haploid set). The released polar body may or may not divide again.
- The secondary oocyte enters meiosis II, but does not complete it. The oocyte remains arrested at metaphase II during the process of ovulation.
- Only after fertilization, the secondary oocyte resumes meiosis II and form an ovum by releasing a second polar body.
- Eventually, the nuclear membrane of the ovum fuses with that of spermatozoa to form a zygote with a complete set of chromosomes (2n).

VALUE ADDITION: VIDEO

Heading text: Oogenesis
Body text: Watch the video clip 3D-animated in the link given below and see how oogenesis and folliculogenesis occurs:

https://www.youtube.com/watch?v=gTSUWHWe70Q
**Value Addition : Interesting to know!!!**

**Heading text:** Difference between male and female gametogenesis

<table>
<thead>
<tr>
<th>SPERMATOCYTOGENESIS</th>
<th>OOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gametogenesis - the process of formation of spermatozoa, including both spermatocytogenesis and spermiogenesis.</td>
<td>Female gametogenesis - the production or development of an ovum.</td>
</tr>
<tr>
<td>No meiotic divisions during fetal period</td>
<td>Primitive germ cell enter into meiosis (arrested at diplotene) during fetal period</td>
</tr>
<tr>
<td>It is a continuous process and completes approximately in 74 days.</td>
<td>It is a discontinuous process and completed in few days to few years</td>
</tr>
<tr>
<td>Although from puberty to old age sperm cells are constantly being generated, the production is subject to extreme fluctuations regarding both quantity and quality.</td>
<td>Using up the oocytes generated before birth. Continual decrease of the oocytes, beginning with the fetal period and complete exhaustion at menopause.</td>
</tr>
<tr>
<td>A spermatogonium forms four functioning small spermatozoa (head 4µm)</td>
<td>An oogonia forms only one large ovum (diameter 120µm).</td>
</tr>
<tr>
<td>No polar bodies are formed.</td>
<td>Polar bodies are formed.</td>
</tr>
<tr>
<td>It is generally completed in the testes and thus mature sperms are released from the testes.</td>
<td>Oocyte arrested at metaphase II are released from the ovary and oocyte maturation is required which is completed in reproductive tract.</td>
</tr>
</tbody>
</table>

**Mammalian sperms**
- A sperm is made up of four parts: a head, neck, middle piece and a tail.
- Small amount of cytoplasm is

**Mammalian ovum**
- Ovum is alecithal and has an exocentric nucleus.
- Large amount of cytoplasm is
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- Nucleus condensed with no nucleoplasm.
- Centriole is present
- Sperm is flagellated and motile
- Surrounded by only plasma membrane.

- Nucleus is bloated with nucleoplasm and is called germinal vesicle.
- Centriole is absent
- Ovum is spherical and non-motile.
- Surrounded by a number of egg envelopes such as zona pellucida.

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**Fig. 3 The process of oogenesis**
(source: [http://commons.wikimediaw.org/wiki/File:Figure_28_02_03.JPG](http://commons.wikimediaw.org/wiki/File:Figure_28_02_03.JPG))
VALUE ADDITION: DID YOU KNOW?

Heading text: The life span of oocytes

Body text: The number of germ cells that arrive at the genital ridge (future ovaries) is not more than few hundred; however, they divide rapidly to form 10,000 oogonia by six weeks of gestation. The number further rises to 600,000 by the eighth week and to 6-7 million by twentieth week of gestation. However, after 20th week (midgestation), the number of oocytes rapidly decline for two reasons; first is decreasing rate of oogonial mitosia and second is extensive oogonial atresia. Thus, from midgestation onwards the progressive decline in germ cell number leaves only 700,000 primordial follicles at birth. This number decreases further to approximately 300,000 by the onset of puberty. Out of these only 400-500 ovulate in the entire course of reproductive life span. (Fig.4)

![Graph showing the number of female germ cells](image)

**Fig 4.** The pool of primordial follicle reaches its maximum around 20 weeks of gestational period and then decrease in a logarithmic fashion throughout the life until complete depletion occurs around the age of menopause (Fig. 4). Reproductive life is initiated when less than 10% (0.5 million) of primordial follicles are left.

Source:Author

**Folliculogenesis**
The process by which the primordial follicles grow into a preovulatory follicle is termed as folliculogenesis. This follicular growth is tightly coordinated with oogenesis. During folliculogenesis, the sequential changes in the morphology of the follicle are described in Fig. 5 and Fig.6.
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In a primordial follicle, the oocyte is surrounded by a single non-dividing layer of granulosa cells covered by a basal lamina. The primordial follicles are 0.03 to 0.05 mm in size.

The non dividing cuboidal cells of primordial follicle differentiate into dividing and secretory columnar cells and now the follicle is termed as primary follicle (diameter 0.1 mm).

With the proliferating granulosa cells, multiple layers are formed surrounding the oocyte. The stromal cells in connection with the granulosa cells also differentiate into thecal cells; the follicle is now termed as secondary follicle (diameter 0.2 mm). With the formation of secondary follicles, the granulosa cells also acquire the receptors to bind gonadotropins.

Various secretions from granulosa cells starts accumulating in the intercellular spaces of the secondary follicle, the secretions eventually accumulate and form a fluid filled cavity in between the granulosa cells called as antral cavity (antrum) and the fluid is called as follicular fluid. The follicle with oocyte surrounded by multiple layers of granulosa cells, layer of thecal cells and with an antral cavity is termed as tertiary follicle or early tertiary follicle. On the basis of its size it is divided into five classes.

- Class 1 follicles are 0.2 mm in diameter,
- Class 2 about 0.4 mm,
- Class 3 about 0.9 mm,
- Class 4 about 2 mm,
- Class 5 about 5 mm. At this stage, the thecal cells also differentiate into theca interna and fibrous theca externa.

The late tertiary follicle is even bigger in size. The granulosa cells in these follicles are differentiated into three types based on the distance from the oocyte. The layer of granulosa cells surrounding the oocyte is termed as corona radiata. The layer far away from oocyte, close to the basement membrane is termed as mural granulosa or membrana granulosa. The layer of granulosa cells that connects corona radiata and mural granulosa is termed as cumulous oophorous. At this stage the follicle is also termed as Graafian follicle. On the basis of size tertiary follicle is divided into class 6 (10mm), class 7 (16mm) and class 8 (20mm).

The final stage of follicular growth is termed as preovulatory follicle (>20mm). At this stage, the follicle undergoes ovulation. Until the preovulatory stage, the follicle contains a primary oocyte that is arrested in prophase of meiosis I. During the late preovulatory stage, the oocyte continues meiosis and becomes a secondary oocyte, arrested in metaphase II. There is only one preovulatory follicle in the ovary at a time.

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**VALUE ADDITION**

**HEADING TEXT: IMPORTANCE OF THECAL CELLS**

**Body text:** Theca cells function in a diverse range of necessary roles during folliculogenesis; to synthesize androgens, provide crosstalk with granulosa cells and oocytes during development, and provide structural support of the growing follicle as it progresses through the developmental stages to produce a mature and fertilizable oocyte. Thecal cells are thought to be recruited from surrounding stromal tissue by factors secreted from an activated primary follicle. The precise origin and identity of these recruiting factors are currently not clear, but it appears that thecal recruitment...
and/or differentiation involves not just one signal, but a complex and tightly controlled combination of multiple factors. It is clear that thecal cells are fundamental for follicular growth, providing all the androgens required by the developing follicle(s) for conversion into estrogens by the granulosa cells. Their function is enabled through the establishment of a vascular system providing communication with the pituitary axis throughout the reproductive cycle, and delivering essential nutrients to these highly active cells. During development, the majority of follicles undergo atresia, and the theca cells are often the final follicular cell type to die. For those follicles that do ovulate, the theca cells then undergo hormone-dependent differentiation into luteinized thecal cells of the corpus luteum.

**Source:** Author

**Fig. 5** Ovarian follicles. a) Primordial follicles. Primary oocytes are surrounded by a layer of flattened granulosa cells. b) Primary follicle. The oocyte is surrounded by a layer of cuboidal granulosa cells. c) Secondary follicle. The oocyte is surrounded by the early zona pellucida and many layers of granulosa cells. d) Early antral follicle. The oocyte is surrounded by many layers of granulosa cells with accumulation of intercellular follicular fluid and a fully formed layer of zona pellucida. Theca interna and theca externa are clearly visible. e) Graafian follicle. The oocyte is surrounded by layers of cumulous cells. Follicular fluid has accumulated forming a large antrum.
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Primordial follicle
- Oocyte
- Flat granulosa cells

Primary follicle
- Oocyte

Early stage
Secondary follicle
- Columnar granulosa cells
- Multiple layers of Granulosa cells
- Theca cells

Secondary follicle
- Antrum
- Theca externa
- Theca interna

Early antral follicle
- Mural granulosa
- Cumulus oophorus
- Corona radiata
- Large antrum

Pre-ovulatory follicle

Ovulation
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Fig.6 Stages of Folliculogenesis Source 

VALUE ADDITION

Heading text: Time-span in growth trajectory of a follicle

Body text: The entire process of folliculogenesis (formation of preovulatory follicle from primordial follicle) takes at least three months.

Fig. 7 Growth trajectory of follicle
Source: http://commons.wikimedia.org/wiki/File:Folliculogenesis_chart.gif

The entire growth trajectory of the follicle takes at least 3 months. Follicle growth up to the antral stage occurs during fetal life and infancy. While the role of gonadotropins in early follicular development remains controversial, the last 2 weeks of development are FSH dependent. The intercycle rise in Follicle-stimulating Hormone (FSH) and decreasing levels thereafter are crucial for recruitment of a cohort of healthy, early antral follicles
and subsequent single dominant selection. Following puberty, anovulation may persist for years and this may presage the development of adult anovulatory infertility. The menopause is preceded by a period of reduced fertility.

Folliculogenesis can be divided into two phases: one gonadotropin independent phase and other gonadotropin dependent phase. Follicular growth up to the formation of secondary follicle is independent of gonadotropin. The granulosa cells in secondary follicle become responsive to gonadotropins. The formation of antral follicle and their growth up to preovulatory follicle followed by ovulation are the gonadotropin dependent stages of folliculogenesis. (Fig.8)

**Gonadotropin independent phase of folliculogenesis**
The pool of primordial follicles is known to be maintained in a dormant state by various forms of inhibitory signals and molecules which are not regulated by gonadotropins. Loss of function of any of these inhibitory molecules of follicular activation, leads to premature and irreversible activation of the primordial follicle pool.

Many years of research have demonstrated that complex bidirectional signaling between the oocyte and the surrounding somatic cells, involving specific cytokines and growth factors are required to control of primordial follicle activation. In contrast, the intracellular signalling pathways activated during follicle development remain largely uncharacterized and are fundamental to understand the molecular systems responsible for ensuring timely delivery of functional oocytes for fertilization.

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**Fig.8** The transition of the follicle from the preantral to early antral stage is the "penultimate" stage of development in terms of gonadotropin (Gn) dependence and follicle destiny (growth versus atresia).

**Source**
Physiology of the ovary

Cytokines involved in primordial to primary follicle transition (Fig.9)

Facilitate primordial follicle recruitment
1. SCF/KL (Stem Cell Factor/Kit Ligand) - Released from granulosa cells and
   a) initiates oocyte growth in primordial follicle
   b) stimulates thecal cells mitosis
   c) maintains growth of preantral and antral granulosa cells
   d) boosts androgen release from thecal cells.
2. FGF2/KGF (Fibroblast Growth Factor) - Released from primordial granulosa
   cells and growing oocyte
   a) promotes recruitment of primordial follicle
   b) suppresses granulosa cell apoptosis
   c) stimulates theca-interstitial cells
3. BMP7 (Bone Morphogenetic Factor 7) - Released from precursor thecal cells
   a) Promotes granulosa cell mitosis
4. BMP4 (Bone Morphogenetic Factor 4) - Released from stromal cell
   a) Promotes oocyte maturation
5. KGF (Keratinocyte Growth Factor) - Released from stromal cells
   a) Promotes thecal cell formation and granulosa cell proliferation
6. LIF (Leukemia Inhibitory Factor) - Released from primordial follicle Oocyte
   a) Stimulate precursor thecal cell and granulosa cell proliferation
GDNF (Glial Cell Derived Neurotropic Factor) - Released from primordial
   a) follicle granulosa cells and the oocyte and stimulate oocyte maturation.

Antagonize follicle recruitment
1. MIH/AMH (Mullerian Inhibiting Hormone/ Anti Mullerian Hormone) -
   Released from granulosa cells up to early antral stage
   a) Depresses recruitment of primordial and preantral follicles
2. CXCL12/SDF1 Chemokine (C-X-C motif) ligand 12/ Stromal Cell
   Derived Factor 1 - Released from granulosa cells and oocyte of primordial
   follicle
   a) Suppress follicle recruitment by its inhibitory action on oocyte as well as
      granulosa cells of primordial follicle.
However, removal of the pituitary (hypophysectomy) prevents the completion of antral follicle development. In the absence of gonadotropins the recruited follicles undergo Atresia*. 

**Gonadotropin dependent phase of folliculogenesis**

Atresia is prevented by gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones bind to follicular FSH and LH receptors that first appear on cells in the late preantral and early antral follicles. FSH alone is sufficient for initial follicular growth, but LH assists further antral expansion. Thus, FSH-knockout mice arrest follicular development preantrally, whereas LH knockout mice block at the antral stage. So, the gonadotropins pick-up preantral follicles and stimulate antral growth.

The basic molecular mechanism by which FSH and LH rescue preantral follicle from atresia is through stimulating the steroid synthesis. When the distribution of receptors in early antral follicles is analyzed, it is found that only the cells of the theca interna bind LH whereas only the granulosa cells bind FSH. Moreover, the effects of hormone binding at each of these sites produce very different consequences. On stimulation with LH, the thecal cells synthesize androgens from acetate and cholesterol. In contrast, the granulosa cells from antral follicle do not express LH receptors and are incapable of forming androgens.

If, however, the granulosa cells are supplied with exogenous androgens, they possess enzymes called aromatase, which aromatize androgens to oestrogens. This aromatization is stimulated by FSH. The production of androgens and estrogens from two different cells i.e. by theca and granulosa cells, respectively, under the influence of two different gonadotropins LH and FSH is termed as “two cell two gonadotropin hypothesis” (Fig. 10).

The two-cell, two-gonadotropin
According to the hypothesis, estrogen synthesis occurs in the following steps:

**Step 1.** LH stimulates the theca cell, through the adenylyl cyclase pathway, to increase the synthesis of LDL receptors and the side-chain-cleavage enzyme.

**Step 2.** Thus stimulated, the theca cell increases the synthesis of androstenedione.

**Step 3.** The androstenedione synthesized in the theca cells freely diffuses to the granulosa cells.

**Step 4.** FSH, also acting through the adenylyl cyclase pathway, stimulates the granulosa cell to produce aromatase.

**Step 5.** The aromatase converts androstenedione to estrone. $17\beta$-HSD then converts the estrone to estradiol. Alternatively, $17\beta$-HSD can first convert the same androstenedione to testosterone, and then the aromatase can convert this product to estradiol. By these pathways, theca-derived androgens are converted to estrogens in the granulosa cell.

**Step 6.** The estradiol diffuses into the blood vessels.

Thus, in the ovary, androgens produced by developing follicles are derived exclusively from thecal cells and the oestrogens arise from granulosa cells. However, progesterone can be produced by both the cell types.

Antral follicles also account for 30–70% of the circulating androgens found in women, mainly androstenedione and testosterone (the remainder coming from the adrenal). The antral follicles produce and release increasing amounts of steroids as they grow (Fig. 10).

In addition, to their release systemically via secretion into the blood, androgens also have important local intrafollicular roles as following:

1) They serve as substrates for conversion to estrogens.
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2) Acting with FSH, they stimulate the proliferation of granulosa cells and thereby follicular growth.
3) They stimulate aromatase activity, thereby promoting estrogen synthesis. Thus, the rising thecal levels of androgens stimulate a massive increase in estrogen biosynthesis. Since the estrogens are mitogens (the molecules which induce mitosis) through autocrine mode of action, they stimulate granulosa cells to proliferate. Thus, a powerful positive feedback system is operating that culminates in a surge, in this case a surge of circulating oestrogens towards the end of antral expansion from the most advanced follicle(s).

Molecular mechanism of FSH action
The granulosa cells secrete insulin like growth factor 1 or 2 (IGF1or 2) depending on the species. The IGF appears to mediate both
a) the stimulation by LH of androgen output by the thecal cells and
b) its FSH-dependent aromatization to oestrogen by granulosa cells.
FSH regulates the availability of IGF to promote follicular development by following three ways
- Stimulating its production by granulosa cells.
- Suppressing the ovarian endogenous release of IGF-binding proteins (IGFBPs).
- Promoting the formation of a protease, called pregnancy-associated plasma protein A (PAPP-A), which cleaves the IGF from its IGFBP, thereby releasing it for action, by granulosa cells.

Gonadotropins and intrafollicular cytokines
Besides steroids, the production and activity of several cytokines are also stimulated by the gonadotrophins during the antral phase to mediate and/or modulate the actions of steroids and gonadotrophin, summarized in table

In particular, the inhibins and activins are of particular importance and well studied. There are two types of inhibins, A and B produced by the granulosa cells. However, whereas inhibin B production is stimulated by FSH, inhibin A is stimulated by both FSH and LH. Thus, the ratio of inhibin A: B rises as the follicle expands to peak at ovulation. Thus, the ratio acts as a marker for follicular expansion, in addition to the rising oestrogen output.
Androgens and oestrogens are particularly important for follicular growth and maturation, but progesterone assumes major significance only as ovulation approaches.

Cytokines that promotes antral follicle growth
1. IGF 1 (Insulin like Growth Factor) (pig, rat), IGF 2 (human, cow, sheep)-
   - Release from dividing granulosa cells from antal follicle (rat, pig, human) or
     thecal cells (cow, sheep)
   a) Promotes FSH-induced mitosis
   b) differentiation and estradiol output of granulosa cells
   c) LH-induced androgen synthesis by thecal cells
2. Inhibin B- Released from granulosa cells in early/mid antral follicle (and decline thereafter)
   a) Enhances FSH stimulation of granulosa cells
3. GDF9 (Growth Differentiation Factor)- Released from preantral and antral oocytes
   a) Co-stimulates with FSH granulosa cell mitosis
   b) stimulates estradiol and depresses progesterone output to prevent premature luteinisation
   c) may interact with BMP15
4. Inhibin A-Released from granulosa cells in large antral follicle, preovulatory follicle an luteinized cells
   a) Enhances LH-induced androgen rise in thecal cells a
   b) Progesterone rise in luteinized
5. TGF-β- Released from thecal cells in antral follicles
   a) Inhibits granulosa/thecal cell proliferation but stimulates GC differentiation
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b) Also stimulate production of inhibin and estradiol

**Cytokines that inhibits follicle growth and/or promotes atresia**

1. **Activins**- Released from granulosa cells in preantral phase, declining as follicle matures (can block further growth if stay high)
   a) Promote FSH receptor expression on early granulosa cells
   b) stimulate granulosa cells proliferation
   c) attenuate LH-induced rise in androgen output from thecal cells

2. **IGFBPs (Insulin like Growth Factor Binding Proteins)**-Released from granulosa cells (sheep, pigs); thecal cells (cow). Depressed by FSH higher in atretic follicles
   a) Bind and attenuate IGFs (which can be released through action of IGFBP protease-pregnancy-associated protein A (PAPP-A) made by granulosa cells under FSH control

3. **TNFα (Tumour Necrosis Factor) and leptin**
   a) Promote atresia
   b) Antagonize FSH effects to depress follicle growth and steroidogenesis

**Cytokines involved in dominant follicle selection**

1. **BMP15 (Bone Morphogenetic Protein)**- Released from preantral and antral oocytes
   a) Depresses PAPP-A output and may be involved in selection of dominant follicle

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**VALUE ADDITION**

**Heading text: Important facts**

1. The number of follicles ovulating in any one cycle is characteristic for each species and ranges from one to several hundred.
2. Thus, dominant follicles are characterized by high ratios of both inhibin:activin and IGF:IGFBP
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Ovulation

Under the influence of a brief LH surge the expanding antral follicles enter into preovulatory phase to ovulate. If it does not, the expanded antral follicle dies. The LH surge coincides with the appearance of LH receptors on the outer granulosa cells. The surge of LH affects these advanced follicles in two ways.

1) It causes major changes in both the oocyte and the follicle cells, which results in the oocyte expulsion from the follicle at ovulation.

2) It changes the whole endocrinology of the follicle, which becomes a corpus luteum at ovulation.

The oocyte undergoes major preovulatory changes within 3–12 h of the beginning of a surge of LH (depending on the species). Changes occurring in the oocyte can be listed as:

1) The nuclear membrane surrounding the dictyate chromosomes breaks down.

2) The arrested meiotic prophase ends, many years after its initiation and the chromosome progress through the remainder of the first meiotic division forming a secondary oocyte with half number of chromosomes and releasing first polar body.

3) The chromosome in the secondary oocyte immediately enter the second meiotic division and come to lie on the second metaphase spindle.

4) Then suddenly, meiosis arrests yet again at Metaphase II.

5) The oocyte is ovulated in this arrested metaphase state.

6) This maturation through the arrest and the ovulation is accompanied by a set of cytoplasmic events which are as follows:

Meiotic Cytoplasmic maturation of oocyte

The intimate contact between the oocyte and the granulosa cells of the cumulus is broken by withdrawal of the cytoplasmic processes. The Golgi apparatus of the oocyte synthesizes lysosomal-like granules, which migrate towards the surface of the oocyte to assume a subcortical position as cortical granules. Remarkably, centrioles are lost at pachytene, and thereafter only pericentriolar material (PCM) organizes microtubules (Fig.11). Protein synthetic activity continues at the same rate, but new and distinctive proteins are synthesized. This activity prepares the oocyte for fertilization.

![Fig.11 Meiotic maturation of oocyte during ovulation. Source: http://www2.mrc-lmb.cam.ac.uk/groups/mschuh/thebasics.html](http://www2.mrc-lmb.cam.ac.uk/groups/mschuh/thebasics.html)
IMPORTANT FACTS

If an oocyte is shed from its follicle prematurely, or removed surgically before the completion of these cytoplasmic maturational events, then its ability to undergo fertilization is much reduced. For this reason, in clinical in vitro fertilization programs, human oocytes aspirated from preovulatory follicles are usually cultured for a few hours before addition of spermatozoa. This procedure improves the chances of a complete maturation of the oocyte.

FACTORS REGULATING OVULATION

As mentioned above meiotic and cytoplasmic maturation of the oocyte is stimulated by the surge of LH, yet it is clear that LH cannot, and does not bind to the oocyte itself. Therefore, its effect must be mediated via the cumulus cells of the follicle, where it is thought to act by suppressing cAMP levels.

Preovulatory growth of follicle cells is associated with a major endocrine switch. The preovulatory growth in follicular size is matched by changes in the pattern of steroid secretion. Within 2 h or so of the beginning of the LH surge, there is a transient rise in the output of follicular oestrogens and androgens followed by a decline. This rise coincides with distinctive changes in the thecal layer, which appears transiently stimulated and hyperemic.

The outer cells of the granulosa layer also show a marked change in their properties.

1) They stop dividing and no longer convert androgen to oestrogen, but instead synthesize progesterone.
2) LH stimulates this synthesis of progesterone via the newly acquired LH receptors.
3) The cells have lost, or reduced, their capacity to bind oestrogen and FSH, but gained the capacity to bind progestins.

This acquisition of the capacity to respond to LH by synthesizing progesterone (and then to be self-stimulated by positive feedback) results in an exponential release of progesterone from the follicle, which becomes significant in the human several hours before ovulation, although in most species only just before or immediately after ovulation. This rising progestin output has three important functional consequences.

1) It depresses growth in the less mature developing follicles.
2) It is essential for ovulation itself. Thus, the progesterone inhibitors such as mifepristone (RU486) suppress ovulation and females genetically knockout for progesterone receptors do not ovulate.
3) It promotes the transition to the progestogenic phase of the ovarian cycle.
Molecular events associated with ovulation

A number of proteolytic enzymes are known to dissolve the protein matrix to release ovum. Under LH influence, directly and/or indirectly via progesterone and/or prostaglandins the activity of these enzymes increases especially at a region called stigma from where oocyte flows out along with the follicular fluid. These enzymes are:

1) Members of a large family of matrix metalloproteinases (MMPs-zinc dependent endopeptidases) like collagenase, gelatinase and their natural tissue inhibitors (TIMPs)

2) Members of family of serine proteases such as plasmin and plasminogen activator.

VALUE ADDITION

Heading text: Important facts

In many species, including humans, the ovarian surface is directly exposed to the peritoneal cavity, but in some (e.g. the sheep, horse and rat) a peritoneal capsule or bursa encloses the ovary to varying degrees and acts to retain the oocyte cumulus mass(es) close to the ovary. There they are collected by cilia on the fimbria of the oviduct, which sweep the cumulus mass into the oviducal ostium. The residual parts of the follicle within the ovary collapse into the space left by the fluid, the oocyte and the cumulus cells, and within this cavity a clot forms. Thus, the postovulatory follicle is composed of a fibrin core, surrounded by several collapsed layers of granulosa cells, enclosed within a fibrous outer thecal capsule

Source: Author
Luteinization

As mentioned in the text earlier, the post ovulatory follicle in the ovary collapse and transforms into a corpus luteum which produces progestogens. This transformation is termed as Luteinization, it involves:

1) Within the follicular antrum, the fibrin core undergoes fibrosis over a period of several days.
2) The membrane propria between the granulosa and thecal layers breaks down and blood vessels invade.
3) Both granulosa cells and cells from the theca interna contribute to the corpus luteum, although many thecal cells also disperse to the stromal tissue.
4) The granulosa cells have now ceased dividing and hypertrophy to form large lutein cells, rich in mitochondria, smooth endoplasmic reticulum, lipid droplets, Golgi bodies and, in many species, a carotenoid pigment, lutein, which may give the corpora lutea a yellowish or orange tinge and called granulosa lutein cells. (Fig.13)
5) The thecal cells transformed to smaller lutein cells, produce progesterone and androgens, and seem to be richer in LH receptors called thecal lutein cells.

Fig.13 Corpous Luteum from rat ovary; in luteinized follicle the granulosa cells are luteinized to granulosa lutein cell (relatively bigger in size) and secrete progesterone. While the thecal cells luteinized to form thecal lutein cells which also secret progesterone.

Source Author

VALUE ADDITION

Heading text: Important facts

Body text: In most species, the principal progestogen secreted from the large lutein cells is progesterone, but secretion of significant quantities of $17\alpha$-hydroxyprogesterone
in primates and of 20α-hydroxyprogesterone in the rat and hamster also occurs. In a few species, notably the great apes and humans, and to a lesser extent the pig, the corpus luteum also secretes oestrogens, particularly oestradiol 17β. Its source also seems to be the large luteal cells, using as substrate androgens derived from the small luteal cells (a hangover from granulosa function in preovulatory follicles). In most species (e.g. the monkey, sheep, cow, rabbit, rat and horse), however, the corpus luteum secretes onlytrivial amounts of oestrogen.

Source: Author

The corpus luteum also secretes two other hormones. 1) Inhibin A is secreted in large amounts in higher primates. It acts to promote production of progesterone 2) The second hormone is oxytocin, which comes from the large lutein cells and is important for ‘Luteolysis’

**Luteotrophins: endocrine support of the corpus luteum.**

LH surge is required for initial transformation; however, for maintenance its small amount is required. Also, in some species prolactin and/or progesterone also help in maintenance of corpus luteum.

**Luteolysis: death of the corpus luteum may be active or passive depending on the species**

The life of the corpus luteum in the non-pregnant female varies among species from 2 to 14 days. Luteal regression or luteolysis involves a collapse of the lutein cells, ischemia and progressive cell death with a consequent fall in the output of progestogens. The whitish scar tissue remaining, the corpus albicans, is absorbed into the stromal tissue of the ovary over a period that varies from weeks to months, depending on the species.

Luteolysis can be caused by two ways

1) Withdrawal or inadequacy of the luteotrophic complex (e.g. humans)
2) Active production of a luteolytic factor that brings about normal luteal regression (e.g. rat).

Thus, in latter case, both luteotrophic support and antiluteolytic support are required to sustain the corpus luteum. The major luteolytic substance is prostaglandin F2α released by endometrium.

**The ovarian cycle and the follicular development**

One complete ovarian cycle is the interval between successive ovulations, where each ovulation is preceded by a period of oestrogen dominance. It could be divided into three phases as:

- **Follicular phase**
- **Preovulatory phase**
- **Luteal phase**

A continuous recruitment of developing primordial, preantral and early antral follicles occurs throughout the cycle, a lot of which undergo atresia if not rescued by FSH and LH, which take them through full antral expansion. This doesn’t affect the blood steroid level.
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However, one (or two) of these rescued follicles survive to become the dominant antral follicle, these dominant follicle/s release high levels of oestrogens in the blood-Follicular phase.
This advanced follicle is then converted to a preovulatory follicle by the transient high levels of LH that are measured in the blood at this time. The other antral follicles become atretic- Preovulatory phase
The successful ovulatory follicle forms a corpus luteum, which secretes progesterone and oestrogen, until luteolysis 14 or so days later- the luteal phase. (At this phase, LH and FSH levels are comparatively low and are insufficient to maintain antral development, which is also suppressed by elevated progesterone levels, so follicular atresia occurs.)
After luteolysis, a new cycle then begins as tonic gonadotrophin levels are elevated and progesterone is low.
Two important features emerge from this description of the human ovarian cycle: first, we need to understand what controls the fluctuating levels of gonadotrophin output (this will be discussed in detail in the next chapter); second, the complete antral expansion phase, ovulation and the complete luteal phase occupy one complete ovarian cycle.

The follicular phase of the cycle
Follicular phase corresponds to the proliferative phase of the uterine cycle (menstruation cycle). By convention, the menstrual cycle begins with the first day of menstruation.
Initiation of menstruation is governed by the preceding luteolysis, which results in declining levels of luteal oestrogen, progesterone and inhibin A.
As a consequence, negative feedback inhibition is relaxed, and both FSH and LH levels rise. These rises permit antral growth to proceed, resulting in first the rising output of inhibin B followed by androgens and oestrogens.
As a consequence, negative feedback is gradually re-exerted and so FSH levels fall and LH levels plateau.
The selection of a dominant follicle leads to a further rise in oestrogen (together with their biosynthetically associated androgens), culminating in an oestrogen (and androgen) surge and a switch from inhibin B to inhibin A output under the combined stimulation of LH and FSH.
This output of oestrogen and inhibin A reflects the development of only the most advanced follicle(s), thus, is a measure of nearness to ovulation.

The preovulatory phase
The surge in oestrogens triggers a rapid rise in LH and FSH levels via its positive feedback effect, and ovulation follows.
As a result of follicular collapse, androgen and thus oestrogen outputs fall, and progesterone levels rise.
The LH and FSH levels now fall equally precipitously because, at least in part, they lack a continuing positive feedback stimulus.

The luteal phase of the cycle
The luteal phase of the cycle corresponds to the secretory phase of the uterine cycle. This phase is characterized by rising concentrations of plasma progesterone and 17α-hydroxyprogesterone, which peak around 8 days after the LH surge. The luteinized cells of the corpus luteum also make large amounts of oestrogen and inhibin A.
The progesterone depresses levels of both gonadotrophins (negative feedback), moreover inhibin A is also active in suppressing FSH. Growth of antral follicles is therefore suppressed and so androgens are also at a low level.
At the end of the luteal phase, if conception has not occurred, oestrogens, progesterone and inhibin A decline at luteolysis, the negative feedback effect of these hormones is relaxed and LH and FSH levels start to rise, thereby permitting the rescue of preantral follicles and the initiation of another cycle.
Physiology of the ovary

Fig. 14 Follicular development and the ovarian cycle
http://en.wikipedia.org/wiki/Menstrual_cycle#mediaviewer/File:Figure_28_02_07.jpg
Feedback by steroid hormones and the inhibins regulates the menstrual cycle

Estradiol regulation of gonadotropin secretion
The oestradiol secreted from ovary has dual function in regulating gonadotrophin secretion.
   1) At low circulating levels, it exerts negative feedback control over FSH and LH.
   2) However, at higher levels, maintained for a duration, it exerts positive feedback resulting in gonadotropin surge.

Progestrone regulation of gonadotropin secretion
Progesterone also has two effects.
   1) First, the high plasma concentration of progesterone, such as is seen in the luteal phase (4–8 ng/ml in humans) enhances the negative feedback effects of oestradiol, FSH and LH secretion being held down to a very low level.
   2) Second, the positive feedback effect of oestradiol is blocked.

The inhibins regulate only FSH secretion
Data indicates a role for inhibin in the negative feedback regulation of FSH secretion.

Increase in FSH stimulates development of the Graafian follicles (1) and estrogen production from follicles (Positive feedback). Estrogen levels increase repairing and thickening of endometrium (2). Also, stimulates LH production (Positive feedback). A peak of LH stimulates ovulation, formation of corpus luteum and thus production of progesterone (3) Increase in progesterone maintains endometrium in preparation for fertilization (4). If fertilization does take place progesterone levels remain high and the endometrium is maintained. If fertilization does not occur, the decreasing levels of progesterone cause mensuration to take place. Decrease in progesterone stimulates FSH production (Negative feedback)

Fig. 15 Annotation of the graph of ovarian cycle. Source: Author
Regulation of gonadotropin secretion
The gonadotrophs of anterior pituitary secrete both the gonadotropins; FSH and LH and lactotrophs secrete prolactin, which is involved in regulating ovarian functions. The pituitary lies close to the hypothalamus (a small part of brain) and have both neural and vascular connections with it. The synthesis and secretion of both FSH and LH depend on a gonadotrophin-releasing hormone (GnRH) released by hypothalamus. The GnRH is released as a series of pulses into the portal vessels; it binds to receptors on the gonadotrophs, and drives gonadotrophin secretion in a pulsatile manner. Therefore, alterations in the output of LH and FSH could be achieved by:
  1) increasing or decreasing either the amplitude or the frequency of these pulses of GnRH
  2) modulating the response of the gonadotrophs to the pulses.

Positive and negative feedback are mediated at the levels of both hypothalamus and pituitary
The ovarian hormones influence gonadotrophin output by exerting its effect on two sites
  1) the anterior pituitary: the hormones might regulate FSH and LH secretion by a direct action on the gonadotrophs. This could be achieved by modulating their sensitivity to hypothalamic GnRH pulses via changing GnRH receptor expression/affinity. There are abundant receptors for oestrogens, progestogens and inhibins in the anterior pituitary, emphasizing the potential importance of this site.
  2) the hypothalamus: the ovarian hormones might change the GnRH output signal either directly by affecting the GnRH neurons in the hypothalamus, or indirectly by changing the activity of other neural systems that exert a modulator influence on GnRH release (both GnRH pulse amplitude and frequency). Large regional concentrations of receptors for oestradiol and progesterone exist in different regions of hypothalamus and its surroundings. However, there is no evidence to support a hypothalamic site of action of inhibin.

Regulation at the level of anterior pituitary
Within the anterior pituitary, oestradiol appears to exert its positive feedback effects by:
  1) inducing and maintaining GnRH receptors and
  2) sensitizing the self-priming process whereby GnRH induces its own receptors.
There is less information on the ways in which oestradiol might cause a decrease in gonadotrophin secretion to mediate its negative feedback. Nor is there detailed information on the way that inhibin exerts its selective depressant effect on FSH secretion.

Regulation at the level of hypothalamus
The accurate nuclei and preoptic/anterior hypothalamic areas are rich in oestradiol receptors, and the GnRH content of neurons in this area changes in response to oestradiol. However, GnRH+ve neurons do not express progesterone or oestradiol-α (ERα) receptors, and express ERβ only weakly which suggests that steroid effects on GnRH secretion must be mediated indirectly via other steroid-sensitive neural systems, which then converge onto GnRH neuronal cell bodies or terminals. In particular, it is assumed that different pathways are likely to mediate negative and positive feedback effects.
Among the hypothalamic neural systems most strongly implicated in the regulation of GnRH secretion, key players having steroid receptors are the amino acid γ-amino-butyric acid (GABA), glutamate, opioid peptide β-endorphin, and noradrenaline (norepinephrine) systems. Among the many other transmitters and peptides that have been suggested to influence GnRH secretion, the recently studied peptide kisspeptin seems of particular interest in the context of feedback. However, it remains a puzzle as to how these various...
neural mechanisms, which can affect GnRH secretion and are sensitive to steroid hormones, interact under physiological circumstances to regulate the cyclic changes in GnRH output.

Fig. 16 Summary of ovarian cycle and its feedback regulation
SUMMARY

- Oogenesis is the process of gamete (ovum) formation in the ovary.
- Oogenesis begins in ovary even before a female is born.
- During early fetal development, the primitive germ cells migrate from yolk sac to the ovaries.
- These germ cells differentiate into OOGONIA within the ovaries.
- Oogonia are diploid stem cells which divide mitotically to produce millions of germ cells.
- Even before birth most of these germ cells degenerate by a process called ATRESIA.
- A few however develop into larger cells called PRIMARY OOCYTES that enter prophase of meiosis I but do not complete that until after puberty.
- During this arrested stage of development, each primary oocyte is surrounded by a single layer of flat follicular cells, and the entire structure is termed as PRIMORDIAL FOLLICLE. These follicles lie in the ovarian stroma (cortical region) and are surrounded by a thin layer of basal lamina.
- The progression of the primordial follicle from a quiescent stage through a series of changes in the morphology and gene expression into a preovulatory follicle that undergo ovulation to form corpus luteum is termed as FOLLICULOGENESIS.
- The growing follicle is the main source of hormones in the ovary.
- As follicle grow in size the primary oocyte also complete meiosis I (reductional division) to become haploid secondary oocyte, release a polar body and enter into meiosis II. This process is termed at OOCYTE MATURATION. In preovulatory follicle, the oocyte is arrested at metaphase II.
- OVULATION is the process of releasing secondary oocyte (which is arrested at metaphase II) from preovulatory follicle into oviduct.
- The secondary oocyte only after fusion with spermatozoa (the process termed FERTILIZATION) undergoes completion of meiosis II, releases a polar body and forms zygote.
- The cells in the left out follicle in the ovary undergo differentiation, the process termed as LUTEINIZATION, to form corpus luteum.
- The corpus luteum actively secretes progesterone hormone (in anticipation of pregnancy) under the influence of LUTEOTROPIC COMPLEX and it is maintained throughout or for a duration during pregnancy.
However, in the absence of pregnancy the corpus luteum degenerates after a few days of ovulation to form corpous albicans the process is termed as LUTEOLYSIS. The process of folliculogenesis, ovulation and luteolysis are repeated again and again in the ovary throughout the reproductive age of female. This cycle is termed as OVARIAN CYCLE.

All the processes mentioned here are tightly regulated via HYPOTHALAMUS-HYPOPHYSEAL-GONADAL axis. Any abnormality in any of the above processes can result in an ovulation and infertility.
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GLOSSARY

Atresia: A periodic process of degeneration of immature ovarian follicles and subsequently re-absorption during the follicular phase of the menstrual cycle. Out of 20 follicles maturing each month, a single follicle undergoes ovulation and rest atresia.

Estrogen: A hormone that is primary for women. It causes the uterine wall to thicken monthly, helping spur ovulation. There are different forms of estrogen hormones. The main form is called Estradiol.

Follicle: A round sac, found in the ovary, containing an egg and cells that produce hormones.

Follicle-stimulating hormone (FSH): A hormone, produced by the pituitary gland, which stimulates the growth of the follicle. The hormone is used in medical treatments, contained in injectable ovulation drugs to help spur growth of the follicles.

Folliculogenesis: The process by which the primordial follicles grow into a preovulatory follicle.

Luteinizing hormone (LH): a gonadotropic hormone that is secreted by the anterior pituitary

Luteotrophins: endocrine support of the corpus luteum.

Luteinization: The postovulatory follicle in the ovary collapse and transforms into a corpus luteum, which produces progestrogens. This transformation is termed as Luteinization.

Luteolysis: death of the corpus luteum.

Menstrual cycle: hormonally controlled cyclic changes occurring in female reproductive system resulting in the monthly replacement of the lining of the uterus.

Oocyte: The official medical term for an egg.

Ovary: The ovaries or "egg sacs" are a pair of reproductive organs of female reproductive system. There are two ovaries, located on located in the pelvis, one on each side of the uterus. The ovaries have two functions: they produce eggs (ova) and female hormones.

Ovulation: When an ovary releases an egg into the fallopian tube.

Progesterone: A hormone that helps prepare the lining of the uterus for the implantation of a fertilized egg. It is present during the second half of the menstrual cycle.

Tunica albuginea: a whitish capsule of dense irregular connective tissue located immediately deep to the germinal epithelium.
EXERCISE

A. MULTIPLE CHOICE QUESTIONS

1. At birth, a girl has in her ovaries many..........that have started meiosis but stopped at prophase I.
   a) Primary oocytes
   b) Secondary oocytes
   c) Ova
   d) Oogonia
2. A primary oocyte divides to produce a(n)
   a) Oogonium
   b) Secondary oocyte
   c) Polar body
   d) Both b)&c)
3. A layer of clear viscous fluid deposited around a primary oocyte is called
   a) corona radiata
   b) Cumulous oophorous
   c) Zona pellucida
   d) Primordial follicle
4. In the process of oogenesis, the polar body
   a) Is formed before fertilization
   b) Is formed after fertilization
   c) Normally receives most of the cytoplasm of the cell
   d) Both a) & b)
5. While the follicle is developing, a positive feedback loop occurs in which..........stimulates the follicle, which increases the secretion of..............., which stimulates the secretion of GnRH.
   a) LH, estrogen
   b) FSH, estrogen
   c) LH, progesterone
   d) FSH, progesterone
6. Which of the following ovarian hormones is involved in positive feedback loop with the hypothalamus and the anterior pituitary?
   a) Progesterone
   b) Estrogen
   c) Testosterone
   d) GnRH
7. A positive feedback loop causes a self amplifying cycle wherea physiological change leads to even greater change in the same direction
   a) True
   b) False
8. When a primary follicle enlarges and there are a several layers of granulosa cells, it is called an
   a) Primordial follicle
   b) Primary follicle
   c) Secondary follicle
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d) Tertiary follicle
9. Which of the following has an antrum
   a) Primordial follicle
   b) Primary follicle
   c) Secondary follicle
   d) Tertiary follicle
10. The layer of granulosa cells surrounding the oocyte in a preovulatory follicle is called
   a) Cumulus oophorous
   b) Mural granulosa
   c) Corona radiata
   d) Zona pellucida
11. Progesterone has a negative feedback effect on GnRH and LH
   a) True
   b) False
12. The period of time when secondary sexual characteristics begin to develop and the potential for sexual reproduction is reached is called
   a) Menarch
   b) Puberty
   c) Menopause
   d) Spermatogenesis
13. The first menses is called _____, and the permanent cessation of menses is called _____.
   a) Menarch, Puberty
   b) Menarch, menopause
   c) Menopause, Menarch
   d) Menopause, puberty
14. After ovulation, progesterone is produced by
   a) Corpus albicans
   b) Graafian follicle
   c) Secondary follicle
   d) Corpus luteum
15. State true and false
   a) The initiation of preantral phase of follicular development is under the control of LH
   b) The development of antral follicle depends on the presence of FSH and LH receptors.
   c) Ovulation occurs at day 14 of menstrual cycle.
   d) The period before ovulation is known as luteal phase.
   e) The luteal phase is associated with the large increase in plasma progesterone.
   f) The endometrium proliferates under the influence of progesterone.
16. The primary female sex hormone is
   a) Testosterone
   b) Estrogen
   c) Progesterone
   d) DHEA
17. At which stage of meiosis does the primary oocyte is arrested at birth
   a) Pachytene
   b) Diplotene
   c) Metaphase I
   d) Anaphase I
18. At which stage of meiosis does the secondary oocyte is arrested at ovulation
   a) Metaphase I
   b) Metaphase II
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c) Anaphase II
d) Anaphase I

B. SHORT ANSWER TYPE QUESTIONS

1. Define: a) Ovulation b) Luteolysis c) Atresia d) Primordial follicle e) Antrum

2. Differentiate:  
a) Gonadotropin dependent folliculogenesis and gonadotropin independent folliculogenesis  
b) Oogenesis and Folliculogenesis  
c) Follicular phase and luteal phase  
d) LH and FSH  
e) Estrogen and progestrone

C. LONG ANSWER TYPE QUESTIONS

1. Describe the histology of ovary with a neatly labeled diagram.

2. Write Short notes on:  
a. Folliculogenesis  
b. Regulation of Gonadotropin secretion  
c. Ovarian cycle  
d. Factors regulating ovulation

3. Describe the role of intrafollicular cytokines.

4. Describe Two-cell two-gonadotropin hypothesis with neatly labeled diagram.

5. Describe the factors regulating ovulation.
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- Principles of Anatomy and Physiology-12th Edn-Gerard J. Tortora and Bryan Derrickson-2009
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Further reading


Weblinks:

- http://education.med.nyu.edu/Histology/courseware/modules/fem-repro-sy/female.reproductive.01.html
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