FOLLICULOGENESIS

Development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins.

Reproductive functions  Female

About Folliculogenesis

Folliculogenesis is the progression of a number of small primordial follicles into large preovulatory follicles that enter the menstrual cycle. From the beginning of primordial follicles growth until oocyte maturation in preovulatory follicles oocyte cytoplasmic organelles undergo dynamic alterations that reflect physiological changes and development. Females have hundreds of thousands of oocytes already at the time of birth. However, before birth, some oocytes will die by a process named apoptosis. Apoptosis is likely to be a mechanism for reducing the number of oocytes/ovarian follicles, and females are born with far fewer oocytes than the maximum number reached during fetal life.

Follicular depletion

Recently, few publications have challenged the idea that a finite number of follicles are set around the time of birth. Renewal of ovarian follicles from germline stem cells (originating from bone marrow and peripheral blood) was reported in the postnatal mouse ovary. Studies attempting to replicate these results are underway, but a study of populations in 325 human ovaries found no supporting evidence for follicular replenishment. Researchers at the University of Edinburgh determined that by the time women are 30 years old, only 10% of their non-growing follicles remain. Moreover, as women age, double-strand breaks accumulate in their primordial follicle reserve. DNA double-strand break repair is vital for the maintenance of oocyte reserve, and a decline in efficiency of repair with age plays a key role in the depletion of the ovarian reserve (ovarian aging).
Follicle developmental stages

The ovarian cortex contains follicles at different developmental stages; these can be classified according to size, type and number of granulosa cells, or if they are dependent or not on gonadotrophic hormones:

- **primordial follicles** - dormant, small, only one layer of flat granulosa cells
- **primary follicles** - mitotic cells, cuboidal granulosa cells
- **secondary follicles** - presence of theca cells, multiple layers of granulosa cells
- **early tertiary follicles**
- **late tertiary follicles** - fully formed antrum, no further cytodifferentiation, no novel progress
- **preovulatory follicles** - building growth in estrogen concentration, all other follicles atretic or dead.

The follicles are named preantral or antral follicles, according to the absence or presence of a cavity, respectively. Preantral follicles are usually classified in three stages: primordial, primary or secondary follicles. At the antral stage, most follicles undergo atretic degeneration. However, a few of them reach the preovulatory stage under gonadotropin stimulation. The fate of each follicle is controlled by endocrine and paracrine factors.

The complete development of the follicle culminates in ovulation, which is when the mature cumulus-oocyte complex is released and may be fertilized. The whole process of development, from primordial follicle to early tertiary follicle, takes approximately two months in humans.

The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. The process begins continuously, meaning that at any time the ovary contains follicles in all stages of development:

**Primordial follicles**

Folliculogenesis begins with follicles in a resting state. These small primordial follicles are present in newborn females and are the prevailing follicle type in the adult ovary (Pic.1 a). At 18–22 weeks post-conception, the cortex of the female ovary contains its peak number of follicles (about 4 to 5 million in the average case, but individual peak populations range from 6 to 7 million. These primordial follicles contain:

- immature oocytes surrounded by flat squamous granulosa cells (the support cells) - that surround the oocyte, and they can stay in this resting state for years some until right before menopause. Overall, there are no specialized junctions
between granulosa cells or between them and the oocyte. At this stage, any substance that needs to gain access to the oocyte is incorporated by endocytosis or enters by diffusion through intimate contact between the membranes of granulosa cells and the oocyte.

**Primary follicles**

After puberty, a few primordial follicles will respond to a recruitment signal each day, and will join a pool of immature growing follicles called primary follicles. Primary follicles start with a single layer of granulosa cells, but the granulosa cells then become active and transition from a flat or squamous shape to a rounded, cuboidal shape as they increase in size and proliferate.

**Secondary follicles**

As the granulosa cells divide, the follicles, now called secondary follicles (Pic.1.b) increase in diameter, adding a new outer layer of connective tissue, blood vessels, and theca cells – theca externa, theca interna (cells that work with the granulosa cells to produce estrogens). Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. There are also cortical granules (seen for the first time in secondary follicles). They are small organelles like vesicles containing enzymes that undergo exocytosis upon fertilization. At this time, cortical granules are aligned near the oocyte plasmatic membrane and the release of their contents aims to harden the zona pellucida to prevent polyspermy.

**Tertiary follicles or antral follicles**

A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or antrum. Follicles in which the antrum has become large and fully formed are considered tertiary follicles (or antral follicles). In general, in tertiary follicles, all the oocytes are completely surrounded by the zona pellucida, which is crossed by projections of the granulosa cells that form indentations in the oolemma.

At this time, the organelles have achieved a more even distribution throughout the ooplasm, and elongated mitochondria, lipid droplets and vesicles increase in numbers. That is only reasonable, since oocytes that grow to a bigger size may require larger amounts of the machinery needed to move and store cytoplasmic constituents. Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop (preovulatory follicle) until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. The ovum will now travel down one of the fallopian tubes to eventually be discharged through menstruation, if not fertilized by a sperm
cell, or implanted in the uterus, if previously fertilized.

The most follicles don’t make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis.

**Hormonal control**

Five hormones participate in an intricate process of positive and negative feedback to regulate folliculogenesis (Pic. 2). They are:

- (GnRH) - gonadotropin-releasing hormone
- (FSH) - follicle-stimulating hormone
- (LH) - luteinizing hormone
- estrogen
- progesterone

The hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH. These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH stimulates the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone estradiol, a type of estrogen. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase. The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase.

Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte, in the process called ovulation.
Amenorrhoea
The absence of a menstrual period in women of reproductive age.
Learn more at: www.fertilitypedia.org/therapy/diag/amenorrhoea

Anorexia Nervosa
An eating disorder characterized by the maintenance of a body weight below average, fear of gaining weight, and a distorted body image.
Learn more at: www.fertilitypedia.org/therapy/diag/anorexia-nervosa

Anovulation
Failure of the ovaries to release an oocyte over a period of time generally exceeding 3 months.
Learn more at: www.fertilitypedia.org/therapy/diag/anovulation

Hydrosalpinx
A hydrosalpinx is an abnormal pouch containing liquid in a fallopian tube.
Learn more at: www.fertilitypedia.org/therapy/diag/hydrosalpinx

Menstrual cycle disorders
An abnormal condition in a woman's menstrual cycle.
Learn more at: www.fertilitypedia.org/therapy/diag/menstrual-cycle-disorders

Polycystic ovary syndrome
A condition in which a woman has an imbalance of female sex hormones. This may lead to changes in the menstrual cycle, cysts in the ovaries, trouble g
Learn more at: www.fertilitypedia.org/therapy/diag/polycystic-ovary-syndrome

Premature ovarian failure
The loss of function of the ovaries before age 40.
Learn more at: www.fertilitypedia.org/therapy/diag/premature-ovarian-failure

Biological control

Progesterone
Steroid hormone, secreted by the ovaries, whose function is to prepare the uterus for the implantation of a fertilized ovum and to maintain pregnancy.
Learn more at: www.fertilitypedia.org/edu/biological-control/progesterone
The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles.

Flowchart of the hormonal control of the menstrual cycle

Sources

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