Obstetrics and Gynecology:

The Essentials of Clinical Care

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The Menstrual Cycle

The menstrual cycle can be divided into three phases:
1. Follicular phase
2. Ovulation
3. Luteal phase

Follicular Phase

Follicular development is a dynamic process designed to allow the monthly recruitment of a cohort of follicles, and the selection of one dominant follicle that will release a single mature oocyte each month.

In humans, the average length of the follicular phase ranges from 10 to 14 days (**Fig. 4.1**), and variability in this length is responsible for most of the variation in total cycle length. The follicular phase initiates at the first day of the menses. At this time the levels of gonadal steroids are low, and with the demise of the corpus luteum follicle-stimulating hormone (FSH) levels begin to rise recruiting a cohort of follicles.

In response to FSH, the follicles initiate the secretion of estrogen, which increases through the follicular phase and is responsible for endometrial growth. The rise in estrogen exerts a negative feedback on FSH at the hypophysis (pituitary gland) level.

In addition, the growing follicles produce inhibin B, which also suppresses FSH secretion by the pituitary.

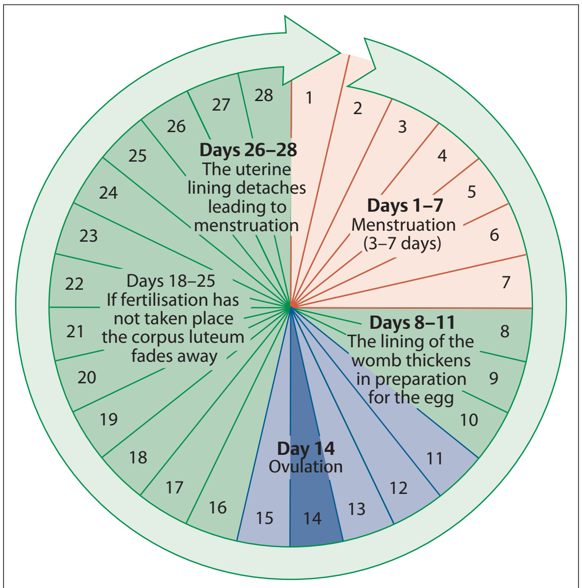

Fig. 4.1 A diagram of the menstrual cycle. The follicular phase constitutes the period beginning with menstruation and ending at ovulation, which is approximately 14 days in most women.

Conversely, the rise in estrogen levels at the beginning of the cycle produces a negative effect on the secretion of luteinizing hormone (LH), but late in the follicular phase LH levels increase dramatically.

During the follicular phase, hormonal feedback promotes the orderly development of a single dominant follicle, which is destined to ovulate from a period of initial growth of a primordial follicle through the stages of the preantral, antral, and preovulatory follicular growth (**Fig. 4.2**).

This phase corresponds to the proliferative phase in the uterus, in which there is building of the endometrial lining. In the middle of the follicular phase of menstrual cycle, after growth of a follicle has been achieved, local concentrations of prostaglandins and proteolytic enzymes induce the extrusion of the oocyte through the follicular wall, and ovulation occurs.

After ovulation, the menstrual cycle enters the luteal phase, the ruptured follicle becomes the corpus luteum and secretion of both progesterone and estrogen provide the adequate environment for the fertilized oocyte to implant in the endometrium. This phase corresponds to the secretory phase in the uterus.

If fertilization occurs, the secretion of human chorionic gonadotropin (HCG) by the embryo rescues the corpus luteum, allowing the continued secretion of progesterone and estrogen to sustain the pregnancy. If fertilization does not occur, the corpus luteum dies, which causes a drop in progesterone and estrogen levels and eventual shedding of the endometrium (menses).

Ovarian Follicular Development

Most oogonia are lost during fetal development, and the remaining follicles are recruited during the reproductive years until menopause occurs, in which the oocyte reserve is depleted.

During fetal development, the oogonia are arrested at the diplotene stage of the prophase in the first meiosis, the germ-cell process of reduction division. At this stage, a single layer of 8 to 10 granulosa cells surrounds the oogonia to form the primordial follicle. Those oogonia that fail to be properly surrounded by granulosa cells undergo atresia.

When the developing oogonia begin to enter the meiotic prophase I, they are known as primary follicles (**Fig. 4.3**), or oocytes, and remain arrested in this phase, until the time of ovulation, by a probable stasis mechanism involving an oocyte maturation inhibitor (OMI) produced by granulosa cells.

It is believed that the inhibitory action of this substance is achieved via gap junctions connecting the oocyte to its surrounding granulosa cells. When the LH surge at midcycle occurs, the gap junctions are disrupted, and the connection between the oocyte and granulosa cells is interrupted, allowing meiosis I to resume.

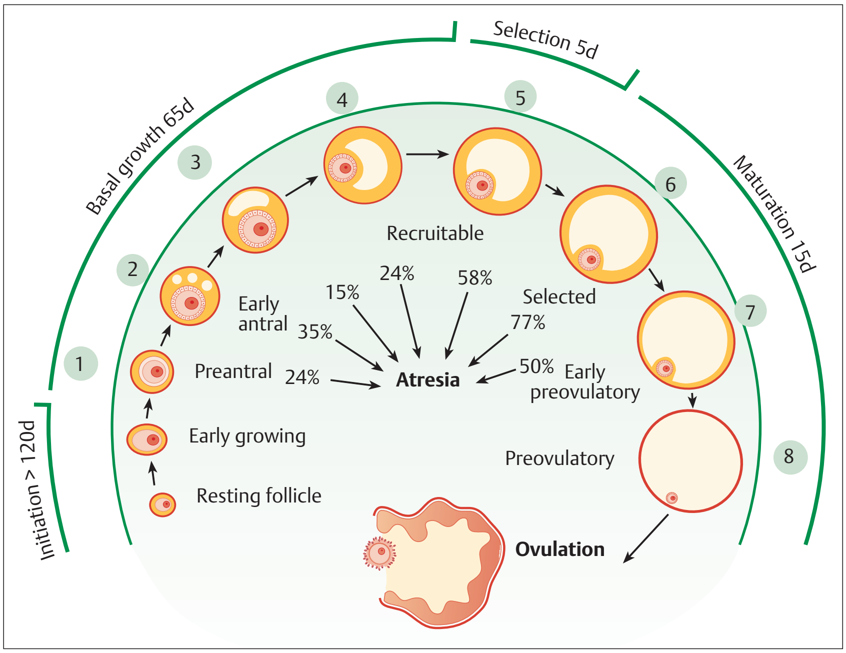

Fig. 4.2 Folliculogenesis and the classes of growing follicles in the human ovary. The early stages of folliculogenesis proceed very slowly, and it has been estimated that in humans the process can take more than 300 days. Even in the preantral stage (class 1), many growing follicles fail to survive, and degenerate through a process termed follicular atresia. Growing follicles enter class 2 usually in the late luteal phase, class 3 between late luteal and early follicular phases, class 4 during late follicular phase, and become recruitable class 5 follicles during late luteal phase.

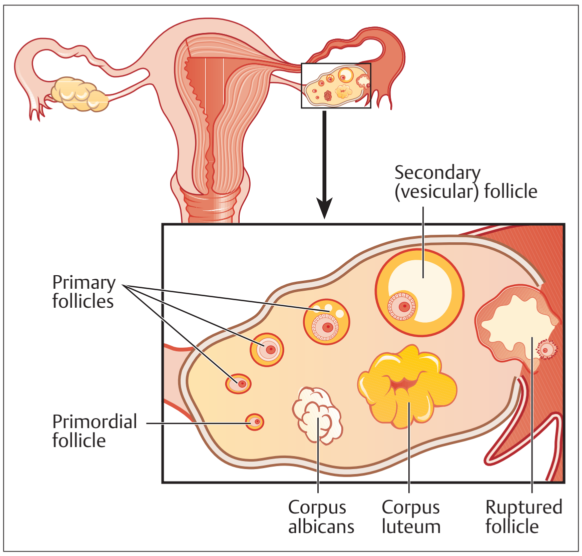

Fig. 4.3 The life cycle of a follicle.

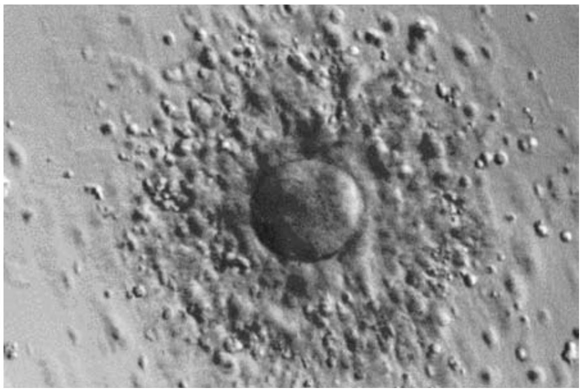

Fig. 4.4 A human oocyte with surrounding granulosa cells, after aspiration.

Primordial Follicles

In each cycle there is growth of a cohort of oocytes. The initial recruitment and growth of the primordial follicles is independent of gonadotropin and affects a cohort over several months. The factor(s) responsible for the recruitment in each cycle is unknown. After initial recruitment, control of follicular growth and differentiation shifts from gonadotropin-independent to gonadotropin-dependent growth, presumably by FSH. The action of FSH promotes growth of the oocyte and expansion of the granulosa cells (**Fig. 4.4**) from a single layer to a multilayer of cuboidal cells.

Preantral Follicle

Driven by the stimulus of FSH, the zona pellucid, a glycoprotein-rich substance, is formed, which separates the oocyte from the surrounding granulosa cells. Simultaneously with the proliferation of granulosa cells, there is proliferation of theca cells in the stroma bordering the granulosa. Both granulosa and theca cells function synergistically to produce estrogen, which is then secreted into the circulation. One of the follicles attains dominance over the rest of the cohort, which undergo atresia.

The mechanism for selection of the dominant follicle is still not clear, but follicular development can be explained by the "two-cell, two-gonadotropin theory," which states that during follicle development, steroid hormone synthesis takes place in a compartmentalized