FOLLICULAR RECRUITMENT, SELECTION, AND DOMINANCE

The term “recruitment” has been used to describe the process by which the follicle departs from the resting pool to initiate growth. However, some authors also use this term to describe the engagement of a cohort of antral follicles into further growth. To avoid confusion, McGee and Hsueh suggested that the first situation be called initial recruitment and the latter, cyclic recruitment.[133] Cyclic recruitment, although obligatory, does not guarantee ovulation because growing follicles are vulnerable to atresia and thus may fall out from the growth trajectory. Selection refers to the process by which the maturing follicular cohort is reduced to a number appropriate for the species-specific ovulatory quota. This process entails negative selection against the subordinate follicles as well as positive selection of the follicles that will determine dominance. Although traditional thinking argues for a single wave of follicular development during the menstrual cycle, recent ultrasound studies suggest that multiple waves of follicular development occur.[134]

In the early follicular phase, no gross morphologic differences exist between the selected follicle and other healthy members of the cohort. However, the leading follicle can be distinguished from other members of the cohort by its size and the high mitotic index of its granulosa cells. Only the leading follicle has detectable levels of FSH in its follicular fluid. The leading follicle also contains significant levels of estradiol, a hallmark of the chosen follicle. Selection does not guarantee progression to ovulation, but given its temporal proximity to this event, ovulation usually does occur.

Dominance refers to the status of the follicle destined to ovulate and its role in regulating the size of the ovulatory quota. The follicle destined to ovulate attains dominance 5 to 7 days after the demise of the corpus luteum of the previous cycle. This conclusion is supported by the observation that the levels of estradiol in the ovarian vein are remarkably different between ovaries by day 5 to 7 of the cycle, attesting to the emergence of the dominant follicle. This follicle continues to thrive under circumstances that it has made inhospitable for competing follicles in both ovaries.

The control of the temporal sequence of events leading up to follicular dominance has been elucidated by ablation studies in infrahuman primates and also in women in which the dominant follicle or corpus luteum was destroyed or removed. Destruction of the largest follicle on day 8 to 12 in the primate ovary delays the next preovulatory surge of pituitary gonadotropins. Conversely, luteectomy in the midluteal phase (days 16 to 19) advances the gonadotropin surge. In women, the interval from ablation of the dominant follicle or corpus luteum to the next ovulation is 14 days. These findings are consistent with the notion that the cyclic structures of the dominant ovary (i.e., the ovary containing the dominant follicle or corpus luteum) are the timekeepers of the menstrual cycle. The 28-day menstrual cycle is thus the result of the intrinsic life span of the dominant follicle (follicular phase) and corpus luteum (luteal phase), not timing dictated by the brain or pituitary.

Studies on primate ovaries indicate that the selection of the follicle destined to ovulate already has occurred as early as day 8 of the cycle.[136] No other member of the follicular cohort is competent to serve as a surrogate for a destroyed follicle, and a timely midcycle gonadotropin surge is not achieved. In the case of the corpus luteum, the next round of follicular growth occurs only after its interference is removed—either naturally (luteolysis) or artificially (luteectomy). Studies on hormone-replaced luteectomized primates suggest that progesterone is the principal agent responsible for the inhibition of follicular growth in the luteal phase.[137] However, inhibin A secreted by the corpus luteum may also play a role in the suppression of FSH and thus follicular maturation. Also central to the process of follicular development is its vasculature. Inhibition of the action of vascular endothelial growth factor (VEGF) blocks follicular maturation secondary to an attenuation of follicular vascular density or reduced vascular permeability, which may limit access of critical growth factors or hormones necessary for follicular growth.[138]

Endocrine Characteristics of Follicles on the Way to Dominance

Follicles with a diameter of less than 8 mm have a relatively low intrafollicular estrogen-to-androgen ratio, but from the midfollicular phase onward, this ratio is reversed (Fig. 8-14). The chosen follicle is able to synthesize estradiol in sufficient quantities to result in appreciable passage of this hormone into the general circulation and asymmetry of ovarian function as early as day 5 to 7 of the cycle.[138-139] In the late follicular phase, the intrafollicular concentrations of estradiol are directly correlated with follicular size and achieve concentrations of approximately 1 μg/mL at a time when circulating estradiol levels reach their peak.[140-141] After the ovulatory surge of LH, intrafollicular concentrations...
of estradiol decline and there is a parallel decrease in the concentration of androstenedione. Concurrently, progesterone and 17α-hydroxyprogesterone concentrations increase, reflecting early granulosa cell luteinization.

**Figure 8-14** Follicular fluid steroid levels and follicular diameter. AD, androstenedione; E2, estradiol; P, progesterone.


Inhibin A concentrations in follicular fluid increase with follicular maturation, whereas inhibin B, activin A, and free follistatin do not show variations with follicular size. Thus, as follicles mature, there is a switch from an environment dominated by activin to one dominated by inhibin A. The increase in inhibin A levels is correlated with increased expression of inhibin A α and β subunit mRNAs in granulosa cells.[142]

Higher follicular fluid concentrations of estrogens and progestogens and lower concentrations of androgens are characteristics of preovulatory follicles.[143] The hormone profiles of smaller follicles late in the follicular phase are characterized by higher concentrations of androgens and lower concentrations of estrogens and progesterone. Antral fluid FSH concentrations tend to be higher in larger follicles compared with serum levels, and estradiol levels are higher in antral fluids marked by measurable levels of FSH. These data are consistent with the concept that follicular hormone concentrations are regulated by the microenvironment of individual follicles. The expression of functional LH receptors
on granulosa cells of the preovulatory primate follicle allows LH to substitute for FSH in the promotion of the terminal stages of maturation.\cite{144}