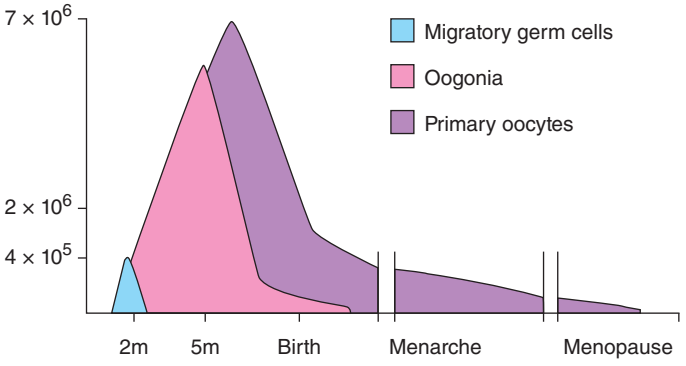

FIGURE 412-2 **Ovarian germ cell number** is maximal at mid-gestation and then decreases precipitously.

of the oocyte and the capacity for hormone secretion. For example, oocyte-derived growth differentiation factor 9 (GDF-9) and bone morphogenic protein-15 (BMP-15), also known as GDF-9b, are required for migration of pregranulosa and pretheca cells to the outer surface of the developing follicle and, hence, initial follicle formation. GDF-9 is also required for formation of secondary follicles, as are granulosa cell–derived KIT ligand (KITL) and the forkhead transcription factor (FOXL2). All of these genes are potential candidates for premature ovarian failure in women, and mutations in the human *FOXL2* gene have been shown to cause the syndrome of blepharophimosis/ptosis/epicanthus inversus, which is associated with ovarian failure.

DEVELOPMENT OF A MATURE FOLLICLE

The early stages of follicle growth are primarily driven by intraovarian factors and may take up to a year from development of the primary follicle to the dominant follicle stage. Further maturation to the preovulatory state, including the resumption of meiosis in the oocyte, requires the combined stimulus of FSH and luteinizing hormone (LH) (Fig. 412-1) and can be accomplished within weeks. Recruitment of secondary follicles from the resting follicle pool requires the direct action of FSH, whereas anti-müllerian hormone (AMH) produced from small growing follicles, restrains this effect of FSH. Accumulation of follicular fluid between the layers of granulosa cells creates an antrum that divides the granulosa cells into two functionally distinct groups: mural cells that line the follicle wall and cumulus cells that surround the oocyte (Fig. 412-3). Recent evidence suggests that, in addition to its role in normal development of the müllerian system, the WNT signaling pathway is required for normal antral follicle development and may also play a role in ovarian steroidogenesis. A single dominant follicle emerges from the growing follicle pool within the first 5–7 days after the onset of menses, and the majority of follicles fall off their growth trajectory and become atretic. Autocrine actions of activin and BMP-6, derived from the granulosa cells, and paracrine actions of GDF-9, BMP-15, BMP-6, and Gpr149, derived from the oocyte, are involved in granulosa cell proliferation and modulation of FSH responsiveness. Differential exposure to these factors may explain the mechanism whereby a given follicle is selected for continued growth to the preovulatory stage. The dominant follicle can be distinguished by its size, evidence of granulosa cell proliferation, large number of FSH receptors, high aromatase activity, and elevated concentrations of estradiol and inhibin A in follicular fluid.

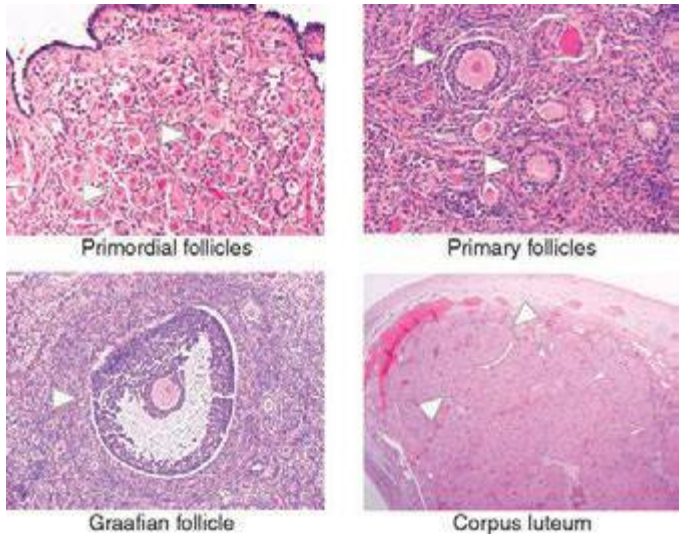

FIGURE 412-3 **Development of ovarian follicles.** The Graafian follicle is also known as a tertiary or preovulatory follicle. *(Courtesy of JH Eichhorn and D. Roberts, Massachusetts General Hospital; with permission.)*

The dominant follicle undergoes rapid expansion during the 5–6 days prior to ovulation, reflecting granulosa cell proliferation and accumulation of follicular fluid. FSH induces LH receptors on the granulosa cells, and the preovulatory, or Graafian, follicle moves to the outer ovarian surface in preparation for ovulation. The LH surge triggers the resumption of meiosis, the suppression of granulosa cell proliferation, and the induction of cyclooxygenase 2 (COX-2), prostaglandins, the progesterone receptor, and the epidermal growth factor (EGF)-like growth factors amphiregulin, epiregulin, betacellulin, and neuroregulin 1, all of which are required for ovulation. EGF-like factors are thought to mediate these follicular responses to LH. Ovulation also involves production of extracellular matrix leading to expansion of the cumulus cell population that surrounds the oocyte and the controlled expulsion of the egg and follicular fluid. Both progesterone and prostaglandins (induced by the ovulatory stimulus) are essential for this process. After ovulation, luteinization is induced by LH in conjunction with the acquisition of a rich vascular network in response to vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF). Traditional regulators of central reproductive control, gonadotropin-releasing hormone (GnRH) and its receptor (GnRHR), are also produced in the ovary and may be involved in corpus luteum function.

REGULATION OF OVARIAN FUNCTION

HYPOTHALAMIC AND PITUITARY SECRETION

GnRH neurons develop from epithelial cells outside the central nervous system and migrate, initially alongside the olfactory neurons, to the medial basal hypothalamus. Studies in GnRH-deficient patients who fail to undergo puberty have provided insights into genes that control the ontogeny and function of GnRH neurons (Fig. 412-4). *KAL1*, *FGF8/FGFR1*, *PROK2/PROKR2*, *NSMF*, and *CDH7*, among others (Chap. 411), have been implicated in the migration of GnRH neurons to the hypothalamus. Approximately 7000 GnRH neurons, scattered throughout the medial basal hypothalamus, establish contacts with capillaries of the pituitary portal system in the median eminence. GnRH is secreted into the pituitary portal system in discrete pulses to stimulate synthesis and secretion of LH and FSH from pituitary gonadotropes, which comprise ~10% of cells in the pituitary (Chap. 401e). Functional connections of GnRH neurons with the portal system are established by the end of the first trimester, coinciding with the production of pituitary gonadotropins. Thus, like the ovary, the hypothalamic and pituitary components of the reproductive system are present before birth. However, the high levels of estradiol and progesterone produced by the placenta suppress hypothalamic-pituitary stimulation of ovarian hormonal secretion in the fetus.

After birth and the loss of placenta-derived steroids, gonadotropin levels rise. FSH levels are much higher in girls than in boys. This rise in FSH results in ovarian activation (evident on ultrasound) and increased inhibin B and estradiol levels. Studies that have identified mutations in *TAC3*, which encodes neurokinin B, and its receptor, *TAC3R*, in patients with GnRH deficiency indicate that both are involved in control of GnRH secretion and may be particularly important at this early stage of development. By 12–20 months of age, the reproductive axis is again suppressed, and a period of relative quiescence persists until puberty (Fig. 412-5). At the onset of puberty,