412 Disorders of the Female Reproductive System

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The female reproductive system regulates the hormonal changes responsible for puberty and adult reproductive function. Normal reproductive function in women requires the dynamic integration of hormonal signals from the hypothalamus, pituitary, and ovary, resulting in repetitive cycles of follicle development, ovulation, and preparation of the endometrial lining of the uterus for implantation should conception occur. It is critical to understand pubertal development in normal girls (and boys) as a yardstick for identifying precocious and delayed puberty.

For further discussion of related topics, see the following chapters: amenorrhea and pelvic pain (Chap. 69), infertility and contraception (Chap. 414), menopause (Chap. 413), disorders of sex development (Chap. 410), and disorders of the male reproductive system (Chap. 411).

DEVELOPMENT OF THE OVARY AND EARLY FOLLICULAR GROWTH

The ovary orchestrates the development and release of a mature oocyte and also elaborates hormones (e.g., estrogen, progesterone, inhibin, relaxin) that are critical for pubertal development and preparation of the uterus for conception, implantation, and the early stages of pregnancy. To achieve these functions in repeated monthly cycles, the ovary undergoes some of the most dynamic changes of any organ in the body. Primordial germ cells can be identified by the third week of gestation, and their migration to the genital ridge is complete by 6 weeks of gestation. Germ cells persist within the genital ridge, are then referred to as *oogonia*, and are essential for induction of ovarian development. Although one X chromosome undergoes X inactivation in somatic cells, it is reactivated in oogonia and genes on both X chromosomes are required for normal ovarian development. A streak ovary containing only stromal cells is found in patients with 45,X Turner's syndrome (Chap. 410).

The germ cell population expands, and starting at ~8 weeks of gestation, oogonia begin to enter prophase of the first meiotic division and become primary oocytes. This allows the oocyte to be surrounded by a single layer of flattened granulosa cells to form a primordial follicle (Fig. 412-1). Granulosa cells are derived from mesonephric cells that invade the ovary early in its development, pushing the germ cells to the periphery. The weight of evidence supports the concept that for the most part, the ovary contains a nonrenewable pool of germ cells. Through the combined processes of mitosis, meiosis, and atresia, the population of oogonia reaches its maximum of 6–7 million by 20 weeks of gestation, after which there is a progressive loss of both oogonia and primordial follicles through the process of atresia. At birth, oogonia are no longer present in the ovary, and only 1–2 million germ cells remain in the form of primordial follicles (Fig. 412-2). The oocyte persists in prophase of the first meiotic division until just before ovulation, when meiosis resumes.

The quiescent primordial follicles are recruited to further growth and differentiation through a highly regulated process that limits the size of the developing cohort to ensure that folliculogenesis can continue throughout the reproductive life span. This initial recruitment of primordial follicles to form primary follicles (Fig. 412-1) is characterized by growth of the oocyte and the transition from squamous to cuboidal granulosa cells. The theca interna cells that surround the developing follicle begin to form as the primary follicle grows. Acquisition of a zona pellucida by the oocyte and the presence of several layers of surrounding cuboidal granulosa cells mark the development of secondary follicles. It is at this stage that granulosa cells develop follicle-stimulating hormone (FSH), estradiol, and androgen receptors and communicate with one another through the development of gap junctions.

Bidirectional signaling between the germ cells and the somatic cells in the ovary is a necessary component underlying the maturation

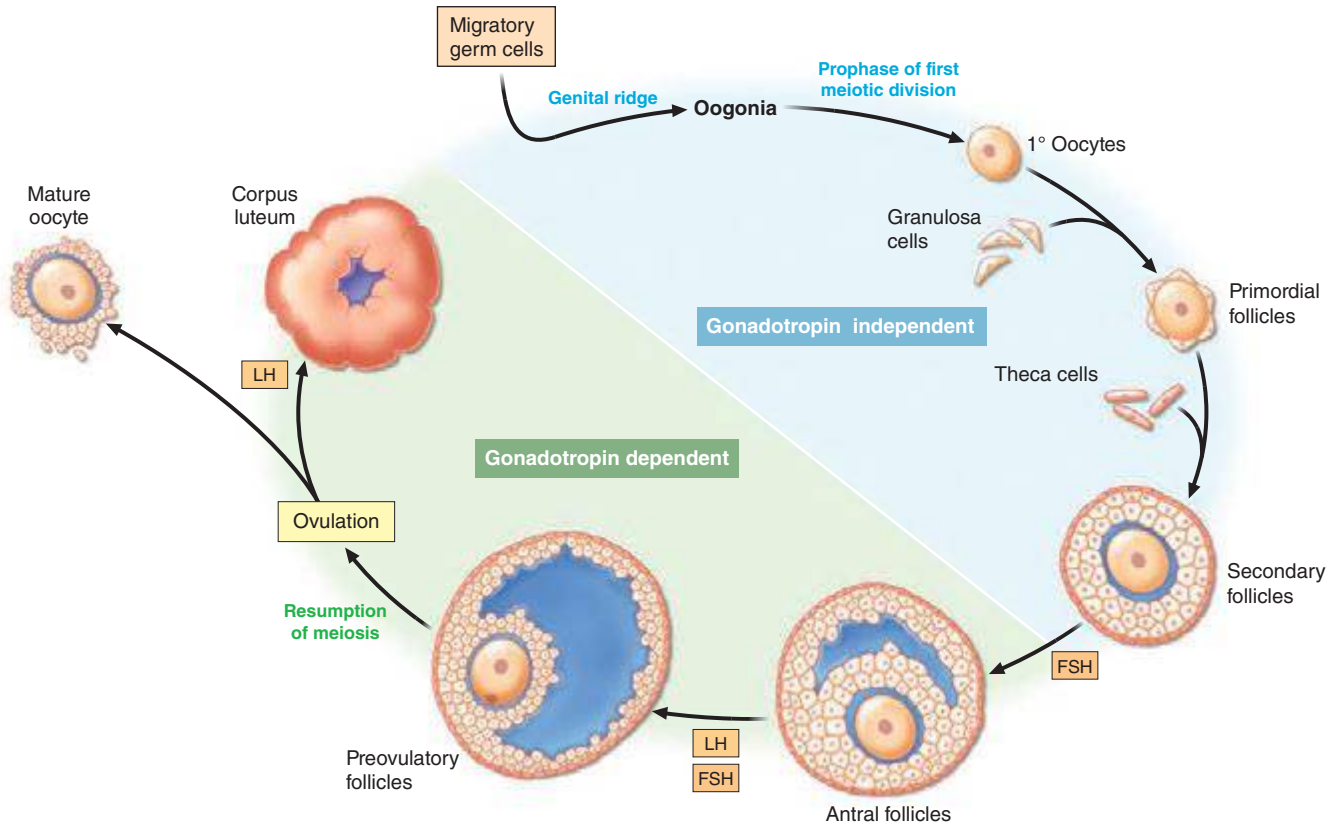

FIGURE 412-1 Stages of ovarian development from the arrival of the migratory germ cells at the genital ridge through gonadotropin-independent and gonadotropin-dependent phases that ultimately result in ovulation of a mature oocyte. FSH, follicle-stimulating hormone; LH, luteinizing hormone.