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detecting AAS use. Illicit testosterone use is detected generally by the measurement of urinary testosterone-to-epitestosterone ratio and further confirmed by the 13C:12C ratio in testosterone using iso tope ratio combustion mass spectrometry. Exogenous testosterone administration increases urinary testosterone glucuronide excre tion and consequently the testosterone-to-epitestosterone ratio. Ratios >6 are highly suggestive of exogenous testosterone use but can also reflect genetic variation. Genetic variations in uri dine diphospho-glucuronyltransferase 2B17 (UGT2B17), the major enzyme for testosterone glucuronidation, affect the testosterone-toepitestosterone ratio. Synthetic testosterone has a lower 13C:12C ratio than endogenously produced testosterone, and these differences in 13C:12C ratio can be detected by isotope ratio combustion mass spectrometry, which is used to confirm exogenous testosterone use in individuals with a high testosterone-to-epitestosterone ratio. PART 12 Endocrinology and Metabolism The treatment of AAS use disorder requires a multidisciplinary team that includes an endocrinologist or an internist to treat the AAS withdrawal hypogonadism and other medical problems; a mental health expert to treat the substance use disorder and depres sive symptoms and to address suicide risk and body image disorder; and sometimes a social worker for care coordination. In patients who are willing to stop or who have already stopped AAS use, the initial step is to restore the hypothalamic-pituitary-gonadal axis by administering either clomiphene (or its enantiomer trans enclomi phene), a partial estrogen agonist, at an initial dose of 50 mg daily or hCG at a dose of 1000–2000 IU three times weekly. Some men may not respond to clomiphene and may require hCG. AAS users also need evaluation and treatment of the underlying body image disor der. Mirror exposure therapy in which the patient stands in front of a mirror and describes his body appearance to the mental health provider has been moderately efficacious in small, randomized trials. Body dysmorphia may require cognitive-behavioral therapy or pharmacotherapy using selective serotonin uptake inhibitors or tricyclic antidepressants. ■ ■FURTHER READING Argenta J et al: Molecular basis of normal and pathological puberty: From basic mechanisms to clinical implications. Lancet Diabetes Endocrinol 11:203, 2023. Bhasin S et al: Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab

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Disorders of the Female Reproductive System 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, result ing in repetitive cycles of follicle development, ovulation, and prepara tion of the endometrial lining of the uterus for implantation should conception occur. For further discussion of related topics, see the following chapters: amenorrhea and pelvic pain (Chap. 405), infertility and contracep tion (Chap. 408), menopause (Chap. 407), disorders of sex develop ment (Chap. 402), and disorders of the male reproductive system (Chap. 403). DEVELOPMENT OF THE OVARY AND EARLY FOLLICULAR GROWTH The ovary orchestrates the development and release of a mature oocyte and secretes hormones (e.g., estrogen, progesterone, inhibins A and B, relaxin) that play critical roles in a variety of target tissues, including breast, bone, and uterus, in addition to the hypothalamus and pitu itary. 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 ges tation. Germ cells persist within the genital ridge, are then referred to as oogonia, and are essential for induction of ovarian development. In patients with 45,X Turner syndrome, primordial germ cells proliferate and migrate to the genital ridge but do not persist because their sur vival requires pregranulosa cells that are dependent on the presence of both X chromosomes (Chap. 402). The germ cell population expands, and starting at ~8 weeks of gesta tion, oogonia begin to enter prophase of the first meiotic division and become primary oocytes. Entry into meiosis provides some degree of protection from programmed cell death. It also allows the oocyte to be surrounded by a single layer of flattened granulosa cells to form a primordial follicle.

Granulosa cells are derived from mesonephric cells that migrate into the ovary early in its development, pushing the germ cells to the periphery. Although there is evidence that both oocyte-like cells and follicle-like structures can form from embryonic stem cells in culture, there is no clear evidence that this occurs in vivo, and thus, the ovary appears to contain a nonrenewable pool of germ cells. Through

7 × 106 Migratory germ cells Oogonia Primary oocytes 2 × 106 4 × 105 Menopause Menarche Birth 5 m 2 m FIGURE 404-1 Ovarian germ cell number is maximal at mid-gestation and decreases precipitously thereafter. the combined processes of mitosis, meiosis, and atresia, the popula tion of oogonia reaches its maximum of 6–7 million by 20 weeks in the fetus, 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. 404-1). 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. Transformation of pri mordial follicles to form primary follicles (Fig. 404-2) 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 sur rounding cuboidal granulosa cells, further surrounded by theca 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 of the oocyte and the capacity for hormone secretion. Members of the trans forming growth factor beta (TGF-β) family of proteins are involved Gonadotropin-Dependent Gonadotropin-Independent Paracrine Control Endocrine Control Inhibin A Inhibin B AMH Preovulatory 20 mm Dominant 11 mm Small Antral 2–5 mm Secondary Primordial Primary Initial Recruitment Cyclic Recruitment Selection Dominance 14 Days

> 120 Days FIGURE 404-2 Gonadotropin-independent and gonadotropin-dependent ovarian follicle development that ultimately results in ovulation of a mature oocyte. AMH, anti-müllerian hormone. (Reproduced with permission from Donna Jeanne Corcoran.)

in this bidirectional signaling; 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 initial follicle formation. GDF-9 is also required for formation of second ary follicles, as are granulosa cell–derived KIT ligand (KITL) and the forkhead transcription factor (FOXL2). A significant number of genes have been identified that are required for development of the normal complement of oogonia in the ovary, initial follicle development, and resistance to follicle loss; all are candidates for premature ovarian insufficiency (POI), and mutations in >50 genes have been identified in patients with POI, with even more that have been associated with an earlier age at natural menopause.

Disorders of the Female Reproductive System CHAPTER 404 DEVELOPMENT OF A MATURE FOLLICLE The early stages of follicle growth are primarily driven by intraovarian factors. Further maturation to the preovulatory stage, including the resumption of meiosis in the oocyte, requires the combined stimu lus of FSH and luteinizing hormone (LH) (Figs. 404-2 and 404-3). Recruitment from the resting pool of secondary follicles, termed cyclic recruitment, requires the direct action of FSH, whereas anti-müllerian hormone (AMH) produced from small growing preantral follicles restrains this effect of FSH, controlling the number of follicles entering the actively growing pool. 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 folli cle wall and cumulus cells that surround the oocyte (Fig. 404-3). As the follicle develops into a preovulatory, or Graffian, follicle, mural granu losa cells in proximity to theca cells express the greatest steroidogenic activity. Cumulus cells surround the oocyte and express mammalian target of rapamycin (mTOR), which regulates cellular metabolism and increases the transfer of nutrients to the oocyte. 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. Recruitment to the small antral stage generally occurs over several cycles with further growth to follicle sizes of >4–7 mm in waves during a single cycle. However, recruitment over a single cycle can occur as evidenced by a normal follicular phase length in gonadotropin-releasing hormone (GnRH)-deficient women in response to a first cycle of treatment with a physiologic regimen of pulsatile GnRH administration and normalization of FSH and LH. A single dominant follicle emerges from the growing follicle pool within the first 5–7 days after the onset of menses, while the majority of follicles Estradiol

PART 12 Endocrinology and Metabolism FIGURE 404-3 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.) 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, and to vas cular endothelial growth factor (VEGF), can alter vascular density and permeability, likely explaining 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 pro liferation, large number of FSH receptors, high aromatase activity, and elevated concentrations of estradiol and inhibin A in follicular fluid. In addition, secretion of estradiol and inhibin from the dominant follicle inhibits FSH and the growth of other follicles. 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), pros taglandins, the progesterone receptor (PR), and the epidermal growth factor–like growth factors amphiregulin, epiregulin, betacellulin, and neuroregulin 1, all of which are required for ovulation. Ovulation requires production of extracellular matrix, leading to expansion of the cumulus cell population that surrounds the oocyte and the con trolled expulsion of the egg and follicular fluid. Both progesterone and prostaglandins (induced by the ovulatory stimulus) are essential for this process, as are members of the matrix metalloproteinase family. After ovulation, luteinization of theca and

granulosa cells is induced by LH in conjunction with the acquisition of a rich vascular network in response to VEGF and basic fibroblast growth factor (FGF). Tradi tional regulators of central reproductive control, GnRH and its recep tor (GnRHR), as well as kisspeptin, are also produced in the ovary and may be involved in corpus luteum function. REGULATION OF OVARIAN FUNCTION ■ ■HYPOTHALAMIC AND PITUITARY SECRETION GnRH neurons derive from cells in the olfactory placode and, to a lesser extent, the neural crest. They migrate into the brain across

the cribriform plate along with the olfactory neurons which then form the olfactory bulb, while the GnRH neurons continue their journey to the hypothalamus. The importance of the initial migra tory pathway into the brain is evidenced in patients born without a nose (bosma arhinia microphthalmia syndrome) who lack olfac tory foramina in the cribriform plate and are both anosmic and have hypogonadotropic hypogonadism. Studies in these and other GnRH-deficient patients who fail to undergo puberty have provided insights into genes that control the ontogeny and function of GnRH neurons (Fig. 404-4). ANOS1 (also known as KAL1), FGF8/FGFR1, Migration Function Hypothalamus KNDY Neural crest KISS1R Olfactory placode KISS1R GnRH1 Pituitary GnRHR FIGURE 404-4 Genetic studies in patients with congenital forms of hypogonadotropic hypogonadism have expanded our understanding of the development and migration of gonadotropin-releasing hormone (GnRH) neurons from the olfactory placode and possibly the neural crest to the hypothalamus as well as the upstream regulation of GnRH secretion by kisspeptin (KISS1), neurokinin B (TAC3), and dynorphin (Dyn), which are co-expressed in the KNDY neurons. GnRHR, GnRH receptor.

PROK2/PROKR2, NSMF, HS6SD1, and CDH7, among a host of others (Chap. 403), have been implicated in the migration of GnRH neurons to the hypothalamus, whereas KISS, TAC3, Dyn, and their receptors are involved in the upstream regulation of GnRH secretion. Approximately 7000 GnRH neurons, scattered throughout the medial basal hypothalamus, establish contacts with capillaries of the pitu itary 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. 390). Functional con nections of GnRH neurons with the portal system are established by the end of the first trimester, coinciding with the production of pitu itary gonadotropins. Thus, like the ovary, the hypothalamic and pitu itary 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. The rise in FSH in girls results in circulating estradiol and inhibin B in what has been termed the mini-puberty of infancy, but without terminal follicle maturation or ovulation. 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 con trol 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. 404-5). At the onset of puberty, pulsatile GnRH secre tion induces pituitary gonadotropin production. In the early stages of puberty, LH and FSH secretion are apparent only during sleep, but as puberty develops, pulsatile LH secretion, a faithful marker of GnRH secretion, occurs throughout the day and night. The mechanisms responsible for the childhood quiescence and pubertal reactivation of the reproductive axis remain incompletely understood. GnRH neurons in the hypothalamus respond to both excitatory and inhibitory factors. Increased sensitivity to the inhibitory influence of gonadal steroids

has long been implicated in the inhibi tion of GnRH secretion during childhood but has not been definitively established in the human. Metabolic signals, including adipocytederived leptin, play a permissive role in reproductive function but are not sufficient to induce puberty (Chap. 413). Studies of patients with isolated GnRH deficiency reveal that mutations in the G protein–coupled receptor 54 (GPR54) gene (now known as KISS1R) preclude the onset of puberty. Kisspeptin, the ligand for this receptor, is derived from the parent peptide, kisspeptin-1 (KISS1), and is a potent stimulant for GnRH release. The tachyki nin 3 gene (TAC3), which encodes neurokinin-B (NKB), stimulates GnRH secretion through kisspeptin signaling, while dynorphin (Dyn), which acts mainly through kappa opioid receptors, plays an inhibitory role in GnRH control. TAC3 and Dyn are frequently coexpressed with KISS1 in KNDy neurons of the median eminence that project to GnRH neurons. This system is intimately involved in both Plasma gonadotropins FSH 50 yr Menopause 10–14 yr Puberty reproductive years Childhood Infancy Birth−20 mo. FIGURE 404-5 Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are increased during the neonatal years but go through a period of childhood quiescence before increasing again during puberty. Gonadotropin levels are cyclic during the reproductive years and increase dramatically with the loss of negative feedback that accompanies menopause.

estrogen and progesterone negative feedback regulation of GnRH secretion as well as metabolic and stress signaling to the reproduc tive axis. Kisspeptin release is pulsatile, and secretion is generated by alternate stimulation and inhibition of kisspeptin by NKB and Dyn, respectively. While pulsatility is an intrinsic property of GnRH neurons, the current model suggests that pulsatile secretion of GnRH is coordinated by pulsatile kisspeptin secretion, with potential input from upstream glutaminergic neurons.

A role for kisspeptin in the onset of puberty is suggested by upregu lation of KISS1 and KISS1R transcripts in the hypothalamus at the time of puberty. The onset of puberty may occur via a switch from epi genetic repression to epigenetic activation in kisspeptin neurons. Two imprinted genes that were initially identified in families with central precocious puberty, MKRN3 and DLK1, may be involved in this switch given their known functions and their association with age at onset of menarche in a large cohort of women. Disorders of the Female Reproductive System CHAPTER 404 While short-term infusion of kisspeptin restored LH pulsatility in patients with hypothalamic amenorrhea and hyperprolactinemia, there is also evidence that tachyphylaxis occurs, potentially limiting its use as a treatment for these conditions. RFamide-related peptides (RFRPs) are the mammalian orthologues of gonadotropin inhibitory hormone (GnIH), which was initially dis covered in the quail. In lower animal species, these peptides decrease gonadal function and sexual motivation in addition to increasing feed ing behavior and mediating the inhibitory actions of stress on repro duction. While RFRP-1 and RFRP-3 neurons send axonal projections to GnRH neurons in humans and RFRPs are secreted into the pituitary portal system, further studies are required to determine their potential physiologic role in the human. ■ ■OVARIAN STEROIDS Ovarian steroid-producing cells do not store hormones but produce them in response to FSH and LH during the normal menstrual cycle. The sequence of steps and the enzymes involved in the synthesis of steroid hormones are similar in the ovary, adrenal, and testis. However, the enzymes required to catalyze specific steps are compartmental ized and may not be abundant or even present in all cell types. Within the developing ovarian follicle, estrogen synthesis from cholesterol requires close integration between theca and granulosa cells—the twocell model for steroidogenesis (Fig. 404-6). FSH receptors are confined to the granulosa cells, whereas LH receptors are restricted to the theca

LH Theca cell pregnenolone Cholesterol 3βHSD progesterone 17 hydroxylase 17-OHP 17,20 lyase Androstenedione 17βHSD Testosterone LH Androstenedione Testosterone Estrone Estradiol FSH aromatase Granulosa cell FIGURE 404-6 Estrogen production in the ovary requires the cooperative function of the theca and granulosa cells under the control of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). HSD, hydroxysteroid dehydrogenase; OHP, hydroxyprogesterone.

cells until the late stages of follicular development, when they are also found on granulosa cells. The theca cells surrounding the follicle are highly vascularized and use cholesterol, derived primarily from circu lating lipoproteins, as the starting point for the synthesis of androstene dione and testosterone under the control of LH. There is some evidence that 11-oxo-androgens, which are generally thought to be produced only in the adrenal, may also be produced to some degree in the ovary. These steroid precursors cross the basal lamina to the granulosa cells, which receive no direct blood supply. The mural granulosa cells are particularly rich in aromatase and, under the control of FSH, produce estradiol, the primary steroid secreted from the follicular phase ovary and the most potent estrogen. Theca cell–produced androstenedione and, to a lesser extent, testosterone are also secreted into peripheral blood, where they can be converted to dihydrotestosterone in skin and to estrogens in adipose tissue. The hilar interstitial cells of the ovary are functionally similar to Leydig cells and are also capable of secret ing androgens. Stromal cells proliferate in response to androgens (as in polycystic ovary syndrome [PCOS]) but do not secrete androgens. However, high levels of androgens may be produced by luteinized theca cells within the stroma in women with hyperthecosis.

PART 12 Endocrinology and Metabolism Development of the rich capillary network following rupture of the follicle at the time of ovulation makes it possible for large molecules such as low-density lipoprotein (LDL) to reach the luteinized granulosa and theca lutein cells. As in the follicle, both cell types are required for steroidogenesis in the corpus luteum. The luteinized granulosa cells are the main source of progesterone production, whereas the smaller theca lutein cells produce 17-hydroxyprogesterone and androgenic substrates for aromatization to estradiol by the luteinized granulosa cells. Production of estrogen metabolites by the corpus luteum plays a significant role in maintenance of the vascularization required for its function. LH is critical for formation and maintenance of corpus luteum structure and function. LH and human chorionic gonado tropin (hCG) bind to a common receptor; thus, in conception cycles, hCG produced upon fertilization rescues the declining function of the corpus luteum, maintaining steroid and peptide secretion for the first 10 weeks of pregnancy. hCG is commonly used for luteal phase support in the treatment of infertility. Steroid Hormone Actions Both estrogen and progesterone play critical roles in the expression of secondary sexual characteristics in women (Chap. 389). Estrogen promotes development of the ductule system in the breast, whereas progesterone is responsible for glandular development. In the reproductive tract, estrogens create a receptive environment for fertilization and support pregnancy and parturition through carefully coordinated changes in the endometrium, thicken ing of the vaginal mucosa, thinning of the cervical mucus, and uterine growth and contractions. Progesterone induces secretory activity in the estrogen-primed endometrium, increases the viscosity of cervical mucus, and inhibits uterine contractions. Both gonadal steroids play critical roles in negative and positive feedback of gonadotropin secre tion. Progesterone also increases basal body temperature, which is used clinically as a marker of ovulation. The vast majority of circulating estrogens and androgens are car ried in the blood bound to carrier proteins, which restrain their free diffusion into cells and prolong their clearance, serving

as a reservoir. High-affinity binding proteins include sex hormone–binding globulin (SHBG), which binds androgens with somewhat greater affinity than estrogens, and corticosteroid-binding globulin (CBG), which also binds progesterone. Modulations in binding protein levels by insulin, androgens, and estrogens contribute to high bioavailable testosterone levels in PCOS and to high circulating total estrogen and progesterone levels during pregnancy. Estrogens act primarily through binding to the nuclear receptors, estrogen receptors (ER) α and β. Transcriptional coactivators and co-repressors modulate ER action (Chap. 389). Both ER subtypes are present in the hypothalamus, pituitary, ovary, and reproductive tract. Although ERα and ERβ exhibit some functional redundancy, there is also a high degree of specificity, particularly in expression within cell types. For example, ERα functions in ovarian theca cells, whereas ERβ

is critical for granulosa cell function. There is also evidence for mem brane-initiated signaling by estrogen. Similar signaling mechanisms pertain for progesterone with evidence of transcriptional regulation through PR-A and PR-B protein isoforms, as well as rapid membrane signaling. ■ ■OVARIAN PEPTIDES Inhibin was initially isolated from gonadal fluids based on its ability to selectively inhibit FSH secretion from pituitary cells. Inhibin is a heterodimer composed of an α subunit and a βA or βB subunit to form inhibin A or inhibin B, both of which are secreted from the ovary. Activin is a homodimer of inhibin β subunits with the capacity to stimulate the synthesis and secretion of FSH. Inhibins and activins are members of the TGF-β superfamily of growth and differentiation fac tors. During the purification of inhibin, follistatin, an unrelated mono meric protein that inhibits FSH secretion, was discovered. Within the pituitary, follistatin inhibits FSH secretion indirectly by binding and neutralizing activin. Inhibin B is constitutively secreted from the granulosa cells of small antral follicles, and its serum levels increase in conjunction with granu losa cell proliferation during recruitment of secondary follicles under the control of FSH (Fig. 404-2). Inhibin B is an important inhibitor of FSH, independent of estradiol, during the menstrual cycle. Inhibin A is present in both granulosa and theca cells and is secreted by the dominant follicle. Inhibin A is also present in luteinized granulosa cells and is a major secretory product of the corpus luteum. Synthesis and secretion of inhibin A are directly controlled by FSH and LH. Although activin is also secreted from the ovary, the excess of follistatin in serum, combined with its nearly irreversible binding of activin, make it unlikely that ovarian activin plays an endocrine role in FSH regulation. However, there is evidence that activin plays an autocrine/ paracrine role in the ovary in germ cell survival, follicle assembly, and inhibition of androgen production, in addition to its intrapituitary role in modulation of FSH production. AMH (also known as müllerian-inhibiting substance) is important in ovarian biology in addition to the function from which it derived its name (i.e., promotion of the degeneration of the müllerian system during embryogenesis in the male). AMH is produced by granulosa cells from small preantral and early antral follicles (Fig. 404-2) and is a marker of ovarian reserve with advantages over inhibin B because of its relative stability across the menstrual cycle. AMH inhibits FSH in the recruitment of primordial follicles into the follicle pool and counters FSH stimulation of aromatase expression. AMH levels increase dur ing puberty, are highest in the early twenties, and decrease markedly by menopause. AMH is increased in PCOS in conjunction with the abundance of small follicles in this disorder. Gonadotropin surge attenuating factor (GnSAF) is an ovarian fac tor that attenuates GnRH-induced gonadotropin secretion. Its role is not yet fully understood, but there is an inverse relationship between GnSAF and follicle size, suggesting that its primary role involves the early stages of follicle development rather than curtailing the gonado tropin surge as its name implies. Relaxin is produced primarily by the theca lutein cells of the corpus luteum. Both relaxin and its receptor, encoded by the gene RXFP1, are

highly expressed in the uterus during the peri-implantation period and its primary role appears to be in promoting decidualization and vascularization of the endometrium prior to implantation. Relaxin was named for its ability to suppress myometrial contractility in pigs and rodents, but it does not appear to exert this activity in women. HORMONAL INTEGRATION OF THE NORMAL MENSTRUAL CYCLE The sequence of changes responsible for mature reproductive func tion is coordinated through a series of negative and positive feedback loops that alter pulsatile GnRH secretion, the pituitary response to GnRH, and the relative secretion of LH and FSH from gonadotropes (Fig. 404-7). The frequency and amplitude of pulsatile GnRH secretion differentially modulate the synthesis and secretion of LH and FSH. Slow GnRH pulse frequencies favor FSH synthesis, whereas increased

KNDy Neuron Hypothalamus GnRH Neuron Estradiol Progesterone GnRH Pituitary Inhibin B Inhibin A Estradiol Estradiol LH FSH Uterus Ovary FIGURE 404-7 The reproductive system in women is critically dependent on both negative feedback of gonadal steroids and inhibin to modulate follicle-stimulating hormone (FSH) secretion and on estrogen positive feedback to generate the preovulatory luteinizing hormone (LH) surge. GnRH, gonadotropin-releasing hormone. GnRH pulse frequency and amplitude favor LH synthesis. FSH syn thesis is also controlled by the activin-inhibin-follistatin system within the pituitary. Activin is produced in both pituitary gonadotropes and folliculostellate cells and stimulates the synthesis and secretion of FSH through autocrine-paracrine mechanisms that are modulated by follistatin, which is also produced in folliculostellate cells. Inhibins function as potent antagonists of activins through sequestration of the activin receptors. Although inhibin is expressed in the pituitary, gonadal inhibin is the principal source of feedback inhibition of FSH. For the majority of the cycle, the reproductive system functions in a classic endocrine negative feedback mode. Estradiol and progesterone inhibit GnRH secretion, acting through kisspeptin and dynorphin in the KNDy neurons, while the inhibins act at the pituitary to selectively inhibit FSH synthesis and secretion (Fig. 404-7). Estradiol also contrib utes to negative feedback at the pituitary with an effect that is greater for FSH than LH. This tightly regulated negative feedback control of FSH is critical for development of the single mature follicle that char acterizes normal reproductive cycles in women. In addition to these negative feedback controls, the menstrual cycle is uniquely dependent on estrogen-induced positive feedback to produce an LH surge that is essential for ovulation of a mature follicle. Estrogen negative feedback in women occurs primarily at the hypothalamus with a small pituitary contribution, whereas estrogen positive feedback occurs at the pitu itary in women with upregulation of GnRH signaling and responsive ness. In women, hypothalamic GnRH secretion plays a permissive role in generating the preovulatory gonadotropin surge, a mechanism that differs significantly from that in rodents and other species that rely on seasonal and circadian cues, in which a surge of GnRH also occurs. ■ ■THE FOLLICULAR PHASE The follicular phase is characterized by cyclic recruitment of a cohort of secondary follicles and the ultimate selection of a preovulatory follicle (Figs. 404-2 and 404-8). The follicular phase begins, by convention, on the first day of menses. However, follicle recruitment is initiated by the rise in FSH that begins in the late luteal phase of the previous cycle in conjunction with the loss of negative feedback of gonadal steroids and likely inhibin A. The fact that an ~20% increase in FSH is

Follicular phase Luteal phase FSH LH Dominant Ovulation Corpus luteum Corpus albicans Secondary Antral Ovarian follicles Inhibin B Disorders of the Female Reproductive System CHAPTER 404 Inhibin A E2 Prog Endo Proliferative Secretory FIGURE 404-8 Relationship between

gonadotropins, follicle development, gonadal secretion, and endometrial changes during the normal menstrual cycle. E2, estradiol; Endo, endometrium; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Prog, progesterone. adequate for follicular recruitment speaks to the marked sensitivity of the resting follicle pool to FSH. The resultant granulosa cell prolifera tion is responsible for increasing early follicular phase levels of inhibin B. Inhibin B, in conjunction with rising levels of estradiol and inhibin A, restrains FSH secretion during this critical period such that only a single follicle matures in the vast majority of cycles. The increased risk of multiple gestation associated with the higher levels of FSH char acteristic of advanced maternal age or with exogenous gonadotropin administration in the treatment of infertility attests to the importance of the precise negative feedback regulation of FSH that is necessary for monofollicular development. With further growth of the dominant follicle, estradiol and inhibin A increase. Increasing levels of estradiol across the follicular phase are responsible for proliferative changes in the endometrium. Acquisition of FSH-induced LH receptors on granu losa cells allows LH to complete the final stages of maturation of the preovulatory follicle, leading to secretion of low levels of progesterone and 17α-hydroxyprogesterone. The exponential rise in estradiol in the mid-late luteal phase results in positive feedback on the pituitary gonadotropes, leading to gen eration of an LH surge (and a smaller FSH surge). The low levels of progesterone secreted from the peri-ovulatory follicle are not required for the gonadotropin surge but appear to play a role in its timing. The LH surge may precede follicle rupture by 24–36 h, during which time the oocyte uncouples from the granulosa cells, and genes involved in inflammation and tissue remodeling are induced. Further alterations in steroidogenesis accompany luteinization of theca and granulosa cells. ■ ■THE LUTEAL PHASE The luteal phase begins with the formation of the corpus luteum from the ruptured follicle (Fig. 404-8). Progesterone, 17α-hydroxyprogesterone, and inhibin A are produced from the luteinized granulosa cells. The granulosa-lutein cells continue to aromatize androgen precursors derived from theca-lutein cells, producing estradiol. The combined actions of estrogen and progesterone, as well as relaxin, are respon sible for the secretory changes in the endometrium that are necessary for implantation. The corpus luteum is supported by LH but has a finite life span. Both the progesterone-induced decrease in LH pulse frequency and diminished postreceptor signaling are likely to con tribute to the demise of the corpus luteum. The progressive decline in hormonal support of the endometrium results in inflammation, local hypoxia and ischemia, and subsequent vascular changes with release of cytokines, cell death, and shedding of the endometrium. If conception occurs, hCG produced by the trophoblast binds to LH receptors on the corpus luteum, maintaining steroid hormone production and preventing involution of the corpus luteum until the luteal-placental shift in hormone production that occurs 6–10 weeks after conception.

CLINICAL ASSESSMENT OF

OVARIAN FUNCTION Menstrual bleeding should become regular within 2–4 years of men arche, although anovulatory and irregular cycles are common before that. For the remainder of adult reproductive life, the cycle length counted from the first day of menses to the day preceding subsequent menses is ~28 days, with a range of 25–35 days. However, cycle-tocycle variability for an individual woman is ±2 days. Luteal phase length is relatively constant between 12 and 14 days in normal cycles; thus, the major variability in cycle length is due to variations in fol licular phase length. The duration of menstrual bleeding in ovulatory cycles varies between 4 and 6 days. There is a gradual shortening of cycle length with age such that women aged >35 years have cycles that are shorter than during their younger reproductive years. Anovulatory cycles increase as women

approach menopause, and bleeding patterns may be erratic.

PART 12 Endocrinology and Metabolism Women who report regular monthly bleeding generally have ovu latory cycles, but several other clinical signs can be used to assess the likelihood of ovulation. Some women experience mittelschmerz, described as midcycle pelvic discomfort that is thought to be caused by the rapid expansion of the dominant follicle at the time of ovulation. A constellation of premenstrual moliminal symptoms such as bloat ing, breast tenderness, mood changes, and food cravings often occur several days before menses in ovulatory cycles, but their absence can not be used as evidence of anovulation. Methods that can be used to determine whether ovulation occurred include a serum progesterone level >3 ng/mL ~7 days after ovulation, an increase in basal body tem perature of 0.24°C (>0.5°F) in the second half of the cycle due to the thermoregulatory effect of progesterone, or detection of the urinary LH surge using ovulation predictor kits, although the mere presence of an apparent LH surge does not guarantee that ovulation will occur. However, because ovulation occurs ~36 h after the LH surge, urinary LH can be helpful in timing intercourse to coincide with ovulation. Ultrasound can be used to detect the growth of the fluid-filled antrum of the developing follicle and to assess endometrial thickness in response to increasing estradiol levels in the follicular phase. It can also be used to provide evidence of ovulation by documenting collapse of the dominant follicle and/or the presence of a corpus luteum as well as the characteristic echogenicity of the secretory endometrium of the luteal phase. PUBERTY ■ ■NORMAL PUBERTAL DEVELOPMENT IN GIRLS The first menstrual period (menarche) occurs relatively late in the series of developmental milestones that characterize normal pubertal devel opment. Menarche is preceded by the appearance of pubic and then axillary hair (adrenarche) as a result of maturation of the zona reticu laris in the adrenal gland and increased adrenal androgen secretion, particularly dehydroepiandrosterone (DHEA). The triggers for adre narche remain unknown but may involve increases in body mass index, as well as in utero and neonatal factors. Menarche is also preceded by breast development (thelarche). The breast is exquisitely sensitive to the very low levels of estrogen that result from peripheral conversion of adrenal androgens and the low levels of estrogen secreted from the ovary early in pubertal maturation. This estrogen sensitivity also explains why infants occasionally develop breast tissue in response to endogenous or environmental estrogens. Breast development precedes the appearance of pubic and axillary hair in ~60% of girls. The interval between the onset of breast development and menarche is ~2 years. There has been a gradual decline in the age of puberty attributed to improved nutrition, however more recent changes indicate a decline in the age of thelarche but not menarche which is associated with obesity. In the United States, menarche occurs at an average age of 12.5 years. Much of the variation in the timing of puberty is due to genetic factors. Heritability estimates from twin studies range between 50 and 80%. Adrenarche and thelarche occur ~1 year earlier in black girls compared with white girls, although the difference in the timing of menarche is less pronounced. Genome-wide association studies

have identified over a hundred genes associated with pubertal tim ing in boys and girls, attesting to the high degree of coordination of this reproductive and growth milestone. These findings include genes involved in GnRH secretion (e.g., TACR3, and the maternally imprinted gene, MKRN3, that has been associated with familial preco cious puberty), pituitary development and function (e.g., POU1F1), hormone synthesis and bioactivity (e.g., STARD4, ESR1, RXRG), gonadal feedback (e.g., INHBA, ESR1), and energy homeostasis and growth, including LIN28B, a sentinel puberty gene, which is a potent regulator of microRNA processing. Other important hormonal changes also

occur in conjunction with puberty. Growth hormone (GH) levels increase early in puberty, stimulated in part by the pubertal increase in estrogen secretion. GH increases insulin-like growth factor-1 (IGF-1), which enhances linear growth. The growth spurt is generally less pronounced in girls than in boys, with a peak growth velocity of ~7 cm/year. Linear growth is ultimately limited by closure of epiphyses in the long bones as a result of prolonged exposure to estrogen. Puberty is also associated with mild insulin resistance. ■ ■DISORDERS OF PUBERTY The differential diagnosis of precocious and delayed puberty is similar in boys (Chap. 403) and girls. However, there are differences in the timing of normal puberty and differences in the relative frequency of specific disorders in girls compared with boys. Precocious Puberty Traditionally, precocious puberty has been defined as the development of secondary sexual characteristics before the age of 8 in girls based on data from Marshall and Tanner in British girls studied in the 1960s. More recent studies led to recommendations that girls be evaluated for precocious puberty if breast development or pubic hair is present at <7 years of age for white girls or <6 years for black girls; however, these guidelines have not been widely accepted in favor of careful follow-up in all girls presenting at <8 years. Precocious puberty in girls is most often centrally mediated (Table 404-1), resulting from early activation of the hypothalamicpituitary-ovarian axis. It is characterized by pulsatile LH secretion (which is initially associated with deep sleep) and an enhanced LH and FSH response to exogenous GnRH or a GnRH agonist (two- to three fold stimulation) (Table 404-2). True precocity is marked by advance ment in bone age of >2 standard deviations, a recent history of growth acceleration, and progression of secondary sexual characteristics. TABLE 404-1 Differential Diagnosis of Precocious Puberty CENTRAL (GnRH DEPENDENT) PERIPHERAL (GnRH INDEPENDENT) Idiopathic CNS tumors Hamartomas Astrocytomas Adenomyomas Gliomas Germinomas CNS infection Genetic, i.e., KISS1, KISS1R, MKRN3, DLK1 Head trauma Iatrogenic Radiation Chemotherapy Surgical CNS malformation Arachnoid or suprasellar cysts Septo-optic dysplasia Hydrocephalus Congenital adrenal hyperplasia Estrogen-producing tumors Adrenal tumors Ovarian tumors Gonadotropin/hCG-producing tumors Exogenous exposure to estrogen or androgen or lavender or tea-tree oil McCune-Albright syndrome Aromatase excess syndrome Abbreviations: CNS, central nervous system; DLK1, delta-like 1 homolog gene; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; KISS1, kisspeptin gene; KISS1R, kisspeptin receptor gene; MKRN3, makorin ring finger protein 3 gene.

TABLE 404-2 Evaluation of Precocious and Delayed Puberty PRECOCIOUS DELAYED Initial Screening Tests History and physical × × Assessment of growth velocity × × Bone age × × LH, FSH × × Estradiol, testosterone × × DHEAS × × 17-Hydroxyprogesterone × TSH, T4 × × Complete blood count × Sedimentation rate, C-reactive protein × Electrolytes, renal function × Liver enzymes × IGF-1, IGFBP-3 × Urinalysis × Secondary Tests Pelvic ultrasound × × Cranial MRI × × β-hCG × GnRH/agonist stimulation test × × ACTH stimulation test × Inflammatory bowel disease panel × × Celiac disease panel × Prolactin × Karyotype × Abbreviations: ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IGF-1, insulin-like growth factor 1; IGFBP-3, IGF-binding protein 3; LH, luteinizing hormone; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone; T4, thyroxine. In girls, centrally mediated precocious puberty (CPP) is categorized as idiopathic in ~85% of cases; however, neurogenic causes must be considered. Loss-of-function mutations in MKRN3 and DLK1, both of which are imprinted genes, have been reported in familial CPP. Activating mutations in KISS1, KISS1R, and PROKR2 have also been found in a small number of patients with CPP. However,

the frequency of these mutations is insufficient to justify their use in routine clinical testing. GnRH agonists that induce pituitary desensitization are the mainstay of treatment to prevent premature epiphyseal closure and preserve adult height, as well as to manage psychosocial repercussions of precocious puberty. Peripherally mediated precocious puberty does not involve activa tion of the hypothalamic-pituitary-ovarian axis and is characterized by suppressed gonadotropins in the presence of elevated estradiol. Management of peripheral precocious puberty involves treating the underlying disorder (Table 404-1) and limiting the effects of gonadal steroids using aromatase inhibitors, inhibitors of steroidogenesis, and ER blockers. It is important to be aware that central precocious puberty can also develop in girls whose precocity was initially peripherally mediated, as in McCune-Albright syndrome and congenital adrenal hyperplasia. Incomplete and intermittent forms of precocious puberty may also occur. For example, premature breast development are common in girls before the age of 2 years, with no further progression and without significant advancement in bone age, estrogen production, or compro mised height. Premature adrenarche can also occur in the absence of progressive pubertal development, but it must be distinguished from late-onset congenital adrenal hyperplasia and androgen-secreting tumors, in which case it may be termed heterosexual precocity. Prema ture adrenarche may be associated with obesity, hyperinsulinemia, and the subsequent predisposition to PCOS.

Delayed Puberty Delayed puberty (Table 404-3) is defined as the absence of secondary sexual characteristics by age 13 in girls. The diagnostic considerations are very similar to those for primary amenor rhea (Chap. 405). Between 25 and 40% of delayed puberty in girls is of ovarian origin, with Turner syndrome accounting for the majority of such patients. Delayed puberty may occur in the setting of systemic illnesses, including celiac disease and chronic renal disease, and endo crinopathies such as diabetes and hypothyroidism. In addition, girls appear to be particularly susceptible to the adverse effects of decreased energy balance resulting from exercise, dieting, and/or eating disorders, and thus, functional hypothalamic amenorrhea (HA) can present with primary amenorrhea. Together, these reversible conditions account for ~25% of delayed puberty in girls. Congenital hypogonadotropic hypo gonadism in girls or boys can be caused by mutations in several differ ent genes or combinations of genes (Fig. 404-4, Chap. 391, Table 404-3).

Disorders of the Female Reproductive System CHAPTER 404 TABLE 404-3 Differential Diagnosis of Delayed Puberty Hypergonadotropic Ovarian Turner’s syndrome Gonadal dysgenesis Chemotherapy/radiation therapy Galactosemia Autoimmune oophoritis Congenital lipoid hyperplasia Steroidogenic enzyme abnormalities 17α-Hydroxylase deficiency Aromatase deficiency Gonadotropin/receptor mutations FSHb, LHR, FSHR Androgen resistance syndrome Hypogonadotropic Genetic Hypothalamic syndromes Leptin/leptin receptor HESX1 (septo-optic dysplasia) PC1 (prohormone convertase) IHH and Kallmann’s syndrome KAL1, FGF8, FGFR1, NSMF, PROK2, PROKR2, SEM3A, HS6ST1, WDR11, CHD7 KISS1, KISS1R, TAC3, TAC3R, GnRH1, GnRHR, and others Abnormalities of pituitary development/function PROP1 CNS tumors/infiltrative disorders Craniopharyngioma Astrocytoma, germinoma, glioma Prolactinomas, other pituitary tumors Histiocytosis X Chemotherapy/radiation Functional Chronic diseases Malnutrition Excessive exercise Eating disorders Abbreviations: CHD7, chromodomain-helicase-DNA-binding protein 7; CNS, central nervous system; FGF8, fibroblast growth factor 8; FGFR1, fibroblast growth factor 1 receptor; FSHβ, follicle-stimulating hormone β chain; FSHR, FSH receptor; GNRHR, gonadotropin-releasing hormone receptor; HESX1, homeobox, embryonic stem cell expressed 1; HS6ST1, heparin sulfate 6-O sulfotransferase 1; IHH, idiopathic hypogonadotropic hypogonadism; KAL, Kallmann; KISS1, kisspeptin 1; KISSR1, KISS1 receptor; LHR, luteinizing hormone receptor; NSMF, NMDA

receptor synaptonuclear signaling and neuronal migration factor; PROK2, prokineticin 2; PROKR2, prokineticin receptor 2; PROP1, prophet of Pit1, paired-like homeodomain transcription factor; SEMA3A, semaphorin-3A; WDR11, WD repeat-containing protein 11.

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