16 - SECTION 2 Sex- and Gender-Based Medicine

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Sex Development PART 12 Endocrinology and Metabolism Sex development begins in utero but continues into young adulthood with the achievement of sexual maturity and reproductive capability. The major determinants of sex development can be divided into three components: chromosomal sex, gonadal sex (sex determination), and phenotypic sex (sex differentiation) (Fig. 402-1). Variations at each of these stages can result in differences (or disorders) of sex develop ment (DSDs) (Table 402-1). In the newborn period, ~1 in 5000 babies undergo investigation because of atypical or ambiguous genitalia. Urgent assessment is indicated, because some causes such as congeni tal adrenal hyperplasia (CAH) can be associated with life-threatening adrenal crises. An experienced multidisciplinary team is important for counseling, planning appropriate investigations, discussing long-term well-being, supporting parents, and providing clear communication about the diagnosis and management options. DSDs can also present at other ages and to a range of health professionals, including with either absent puberty, primary amenorrhea, or androgenization in the teen years (Table 402-2). Other forms of gonadal dysfunction (e.g., Klinefelter syndrome [KS], Turner syndrome [TS]) often are diagnosed later in life by internists. Because DSDs are associated with a variety of psychological, reproductive, and potential medical consequences, an open dialogue must be established between the patient and health care providers to ensure continuity and attention to these issues across the life span. Gender variance and gender dysphoria are more common among some individuals with DSD than in the general population, though not high. Thus, attention to and comfort discussing gender identity is important. Support groups also have a valuable role to play for many patients and families. Care of individuals with DSDs should be holistic, often involving medical, psychosocial, and urogynecologic expertise, while acknowl edging that the best way to care for individuals with DSD is not always clear and should be individualized. There are many controversies, particularly concerning whether genitoplasty or prophylactic gonadec tomy in selected conditions should be performed for infants and young children prior to the age of consent. Accepted nomenclature is also Chromosomal Sex

XX XY Ovary-determining genes Testis-determining genes Gonadal Sex Gonadal steroids & peptides (T, DHT, AMH/MIS) Gonadal steroids (E2) Phenotypic Sex FIGURE 402-1 Sex development can be divided into three major components: chromosomal sex, gonadal sex, and phenotypic sex. AMH, anti-müllerian hormone also known as Müllerian-inhibiting substance, MIS; DHT, dihydrotestosterone;

T, testosterone.

controversial. Previous terms such as intersex and hermaphrodite were changed by the 2006 Consensus Statement to disorder of sex develop ment and ovotesticular DSD. The term “disorder” is often considered negative and stigmatizing and thus has shifted toward difference of sex development, but no term is universally accepted. SEX DEVELOPMENT Chromosomal sex, defined by a karyotype, describes the X and/or Y chromosome complement (46,XY; 46,XX) established at the time of fertilization. The presence of a normal Y chromosome determines that testis development will occur even in the presence of multiple X chromosomes (e.g., 47,XXY). Loss of an X chromosome impairs gonad development (45,X or 45,X/46,XY mosaicism). Fetuses with no X chro mosome (45,Y) are not viable. Gonadal sex refers to the histologic and functional characteristics of gonadal tissue as testis or ovary. The embryonic gonad is initially “bipotential” and can develop into either a testis or an ovary (Fig. 402-2). Testis development is initiated by expression of the gene SRY (sexdetermining region on the Y chromosome) (from ~42 days after conception). Disruption of SRY prevents testis development in 46,XY individuals, whereas translocation of SRY in 46,XX individuals induces testis development and a male phenotype. SRY regulates SOX9 (SRYrelated HMG-box gene 9), leading to expression of a cascade of genes involved in testis development, including in Sertoli cell maturation and Leydig cell differentiation/steroidogenesis. Disruption of some of these genes can influence both the development of the testis and other organs, such as kidney (WT1), adrenal/spleen (SF1, NR5A1), brain (PPP1R12A), or heart (GATA4). Chromosomal segment duplications (e.g., Xp21 containing DAX1/NR0B1) can also impair testis develop ment, revealing the sensitivity of testis-determining pathway to gene dosage effects. Ovarian development is not a “passive” process. Many specific genes are expressed during early ovary development, some of which may repress testis development (e.g., WNT4, R-spondin-1) (Fig. 402-2). Once the ovary has formed, additional factors are required for normal follicular development (e.g., follicle-stimulating hormone [FSH] recep tor). Steroidogenesis in the ovary requires the development of follicles that contain granulosa cells and theca cells surrounding the oocytes (Chap. 404). Thus, there is relatively limited ovarian steroidogenesis until puberty. Germ cells also develop in a sex dimorphic manner. In the develop ing ovary, primordial germ cells (PGCs) show marked proliferation and enter meiosis, whereas they undergo mitotic arrest in the develop ing testis. Approximately 7 million germ cells are present in the fetal ovary toward the end of the second trimester, and 1 million remain at birth. Only 400 are ovulated during a woman’s reproductive life span (Chap. 404). Phenotypic sex refers to the structures of the external and internal genitalia and secondary sex characteristics. In early gestation, internal and external genitalia are initially similar in both sexes (“indifferent”). Sex-specific development occurs as a result of hormone action (Fig. 402-3). The developing testis releases anti-müllerian hormone (AMH; also known as müllerian-inhibiting substance [MIS]) from Sertoli cells and testosterone from Leydig cells. AMH acts through specific receptors to cause regression of the müllerian structures from 60–80 days after conception. At ~60–140 days after conception, tes tosterone supports the maintenance of wolffian structures, including the epididymides, vasa deferentia, and seminal vesicles. Testosterone is the precursor for

dihydrotestosterone (DHT), a potent androgen that promotes development of the external genitalia, including the penis and scrotum (60–100 days, and thereafter) (Fig. 402-3). The urogenital sinus develops into the prostate and prostatic urethra in the male and into the urethra and lower portion of the vagina in the female. The genital tubercle becomes the glans penis in the male and the clitoris in the female. The urogenital swellings form the scrotum or the labia majora, and the urethral folds fuse to form the shaft of the penis and the male urethra or the labia minora. In the female, wolffian ducts regress and the müllerian ducts form the fallopian tubes, uterus, and upper segment of the vagina. A female phenotype will develop in the

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