410 Disorders of Sex Development

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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. 410-1). Variations at each of these stages can result in disorders (or differences) of sex development (DSDs) (Table 410-1). In the newborn period, approximately 1 in 4000 babies require investigation because of ambiguous (atypical) genitalia. Urgent assessment is required, because some causes such as congenital adrenal hyperplasia (CAH) can be associated with life-threatening adrenal crises. Support for the parents and clear communication about the diagnosis and management options are essential. The involvement of an experienced multidisciplinary team is important for counseling, planning appropriate investigations, and discussing long-term well-being. DSDs can also present at other ages and to a range of health professionals. Subtler forms of gonadal dysfunction (e.g., Klinefelter's syndrome [KS], Turner's syndrome [TS]) often are diagnosed later in life by internists. Because these conditions 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.

SEX DEVELOPMENT

Chromosomal sex, defined by a karyotype, describes the X and/or Y chromosome complement (46,XY; 46,XX) that is 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 or 48,XXXY). The loss of an X chromosome impairs gonad development (45,X or 45,X/46,XY mosaicism). Fetuses with no X chromosome (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 bipotential and can develop (from ~42 days after conception) into either a testis or an ovary, depending on which genes are expressed (Fig. 410-2). Testis development is initiated by expression of the Y chromosome gene *SRY* (sex-determining region on the Y chromosome) that encodes an HMG box transcription factor. *SRY* is expressed transiently in cells destined to become Sertoli cells and serves as a pivotal switch to establish the testis lineage. Mutation of *SRY* prevents testis development in 46,XY individuals, whereas translocation of *SRY* in 46,XX individuals is sufficient to induce testis development and a male phenotype. Other genes are necessary to continue testis development. *SOX9* (*SRY*-related HMG-box gene 9) is upregulated by *SRY* in the developing testis but is suppressed in the ovary. *WT1* (Wilms' tumor–related gene 1) acts early in the genetic pathway and regulates the transcription of several genes, including *SF1* (*NR5A1*), *DAX1* (*NR0B1*), and *AMH* (encoding müllerian-inhibiting substance [MIS]). *SF1* encodes steroidogenic factor 1, a nuclear receptor that functions in cooperation with other transcription factors to regulate a large array of adrenal and gonadal genes, including *SOX9* and many genes involved in steroidogenesis. *SF1* mutations causing loss of function are found in ~10% of XY patients with gonadal dysgenesis and impaired androgenization. In contrast, duplication of a related gene *DAX1* also impairs testis development, revealing the exquisite sensitivity of the testis-determining pathway to gene dosage effects. *DAX1* loss-of-function mutations cause adrenal hypoplasia, hypogonadotropic hypogonadism, and testicular dysgenesis. In addition to the genes mentioned above, studies of humans and mice indicate that at least 30 other genes are also involved in gonad development (Fig. 410-2). These genes encode an array of signaling molecules and paracrine growth factors in addition to transcription factors.

Although ovarian development once was considered a "default" process, it is now clear that specific genes are expressed during the earliest stages of ovary development. Some of these factors may repress testis development (e.g., WNT4, R-spondin-1) (Fig. 410-2). Once the ovary has formed, additional factors are required for normal follicular development (e.g., follicle-stimulating hormone [FSH] receptor, *GDF9*). Steroidogenesis in the ovary requires the development of follicles that contain granulosa cells and theca cells surrounding the oocytes (Chap. 412). Thus, there is relatively limited ovarian steroidogenesis until puberty.

Germ cells also develop in a sex dimorphic manner. In the developing ovary, primordial germ cells (PGCs) proliferate and enter meiosis, whereas they proliferate and then undergo mitotic arrest in the developing testis. PGC entry into meiosis is initiated by retinoic acid that activates *STRA8* (stimulated by retinoic acid 8) and other genes involved in meiosis. The developing testis produces high levels of CYP26B1, an enzyme that degrades retinoic acid, preventing PGC entry into meiosis. Approximately 7 million germ cells are present in the fetal ovary in the second trimester, and 1 million remain at birth. Only 400 are ovulated during a woman's reproductive life span (Chap. 412).

Phenotypic sex refers to the structures of the external and internal genitalia and secondary sex characteristics. The developing testis releases anti-müllerian hormone (AMH; also known as müllerian-inhibiting substance [MIS]) from Sertoli cells and testosterone from Leydig cells. AMH is a member of the transforming growth factor (TGF) β family and acts through specific receptors to cause regression of the müllerian structures from 60–80 days after conception. At ~60–140 days after conception, testosterone supports the development 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 (65–100 days, and thereafter) (Fig. 410-3). 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

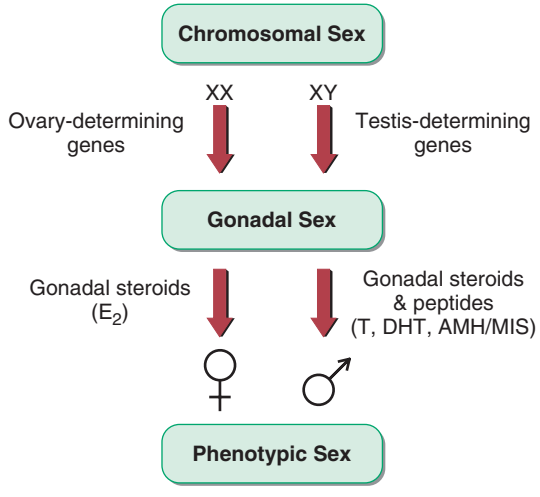

FIGURE 410-1 Sex development can be divided into three major components: chromosomal sex, gonadal sex, and phenotypic sex. DHT, dihydrotestosterone; MIS, müllerian-inhibiting substance also known as anti-müllerian hormone, AMH; T, testosterone.