such situations, gonadectomy usually is considered to prevent further androgen secretion at puberty and prevent risk of gonadoblastoma (up to 25%). Individuals raised as males usually require reconstructive surgery for hypospadias and removal of dysgenetic or streak gonads if the gonads cannot be brought down into the scrotum. Scrotal testes can be preserved but require regular examination for tumor development and sonography at the time of puberty. Biopsy for carcinoma in situ is recommended in adolescence, and testosterone supplementation may be required to support androgenization in puberty or if low testosterone is detected in adulthood. Height potential is usually attenuated; some children receive recombinant growth hormone using TS protocols. Screening for cardiac, renal, and other TS features should be considered, and psychological support offered for the family and young person.

OVOTESTICULAR DSD

Ovotesticular DSD (formerly called *true hermaphroditism*) occurs when both an ovary and a testis—or when an ovotestis—are found in one individual. Most individuals with this diagnosis have a 46,XX karyotype, especially in sub-Saharan Africa, and present with ambiguous genitalia at birth or with breast development and phallic development at puberty. A 46,XX/46,XY chimeric karyotype is less common and has a variable phenotype.

DISORDERS OF GONADAL AND PHENOTYPIC SEX

Disorders of gonadal and phenotypic sex can result in underandrogenization of individuals with a 46,XY karyotype (46,XY DSD) and the excess androgenization of individuals with a 46,XX karyotype (46,XX DSD) (Table 410-1). These disorders cover a spectrum of phenotypes ranging from "46,XY phenotypic females" or "46,XX phenotypic males" to individuals with atypical genitalia.

46,XY DSD

Underandrogenization of the 46,XY fetus (formerly called *male pseudohermaphroditism*) reflects defects in androgen production or action. It can result from disorders of testis development, defects of androgen synthesis, or resistance to testosterone and DHT (Table 410-1).

Disorders of Testis Development • ***TESTICULAR DYSGENESIS*** *Pure* (or *complete*) *gonadal dysgenesis* (*Swyer's syndrome*) is associated with streak gonads, müllerian structures (due to insufficient AMH/MIS secretion), and a complete absence of androgenization. Phenotypic females with this condition often present because of absent pubertal development and are found to have a 46,XY karyotype. Serum sex steroids, AMH/MIS, and inhibin B are low, and LH and FSH are elevated. Patients with *partial gonadal dysgenesis* (*dysgenetic testes*) may produce enough MIS to regress the uterus and sufficient testosterone for partial androgenization, and therefore usually present in the newborn period with atypical genitalia. Gonadal dysgenesis can result from mutations or deletions of testis-promoting genes (*WT1*, *CBX2*, *SF1*, *SRY*, *SOX9*, *MAP3K1*, *DHH*, *GATA4*, *ATRX*, *ARX*, *DMRT*) or duplication of chromosomal loci containing "antitestis" genes (e.g., *WNT4/RSPO1*, *DAX1*) **(Table 410-3)**. Among these, deletions or mutations of *SRY* and heterozygous mutations of *SF1* (*NR5A1*) appear to be most common but still account collectively for <25% of cases. Associated clinical features may be present, reflecting additional functional roles for these genes. For example, renal dysfunction occurs in patients with specific *WT1* mutations (Denys-Drash and Frasier's syndromes), primary adrenal failure occurs in some patients with *SF1* mutations, and severe cartilage abnormalities (campomelic dysplasia) are the predominant clinical feature of *SOX9* mutations. A family history of DSD, infertility, or early menopause is important because mutations in *SF1/NR5A1* can be inherited from a mother in a sex-limited dominant manner (which can mimic X-linked inheritance). In some cases, a woman may later develop primary ovarian insufficiency because of the effect of *SF1* on the ovary. Intraabdominal dysgenetic testes should be removed to prevent malignancy, and estrogens can be used to induce secondary sex characteristics and uterine development in 46,XY individuals raised as females, if it is felt that a female gender identity is established. *Absent (vanishing) testis syndrome* (*bilateral anorchia*) reflects regression of the testis during development. The etiology is unknown, but the absence of müllerian structures indicates adequate secretion of AMH early in utero. In most cases, androgenization of the external genitalia is either normal or slightly impaired (e.g., small penis, hypospadias). These individuals can be offered testicular prostheses and should receive androgen replacement in adolescence.

Disorders of Androgen Synthesis Defects in the pathway that regulates androgen synthesis **(Fig. 410-4)** cause underandrogenization of the 46,XY fetus (Table 410-1). Müllerian regression is unaffected because Sertoli cell function is preserved. Most of these conditions can present with a spectrum of genital phenotypes, ranging from female-typical external genitalia or clitoromegaly in the more severe situations to penoscrotal hypospadias or a small phallus in others.

LH RECEPTOR Mutations in the LH receptor (LHCGR) cause Leydig cell hypoplasia and androgen deficiency, due to impaired actions of human chorionic gonadotropin in utero and LH late in gestation and during the neonatal period. As a result, testosterone and DHT synthesis are insufficient for complete androgenization.

STEROIDOGENIC ENZYME PATHWAYS Mutations in *steroidogenic acute regulatory protein* (*StAR*) and *CYP11A1* affect both adrenal and gonadal steroidogenesis (Fig. 410-4) **(Chap. 406)**. Affected individuals (46,XY) usually have severe early-onset salt-losing adrenal failure and a female phenotype, although later-onset milder variants have been reported. Defects in *3β-hydroxysteroid dehydrogenase type 2* (*HSD3β2*) also cause adrenal insufficiency in severe cases, but the accumulation of dehydroepiandrosterone (DHEA) has a mild androgenizing effect, resulting in ambiguous genitalia or hypospadias. Salt loss occurs in many but not all cases. Patients with CAH due to *17α-hydroxylase (CYP17) deficiency* have variable underandrogenization and develop hypertension and hypokalemia due to the potent salt-retaining effects of corticosterone and 11-deoxycorticosterone. Patients with complete loss of 17α-hydroxylase function often present as phenotypic females who fail to enter puberty and are found to have inguinal testes and hypertension in adolescence. Some mutations in *CYP17* selectively impair 17,20-lyase activity without altering 17α-hydroxylase activity, leading to underandrogenization without mineralocorticoid excess and hypertension. Disruption of the coenzyme, *cytochrome b5* (*CYB5A*), can present similarly, and methemoglobinemia is usually present. Mutations in *P450 oxidoreductase* (*POR*) affect multiple steroidogenic enzymes, leading to impaired androgenization and a biochemical pattern of apparent combined 21-hydroxylase and 17α-hydroxylase deficiency, sometimes with skeletal abnormalities (Antley-Bixler craniosynostosis). Defects in *17β-hydroxysteroid dehydrogenase type 3* (*HSD17β3*) and *5α-reductase type 2* (*SRD5A2*) interfere with the synthesis of testosterone and DHT, respectively. These conditions are characterized by minimal or absent androgenization in utero, but some phallic development can occur during adolescence due to the action of other enzyme isoforms. Individuals with 5α-reductase type 2 deficiency have normal wolffian structures and usually do not develop breast tissue. At puberty, the increase in testosterone induces muscle mass and other virilizing features despite DHT deficiency. Some individuals change gender from female to male at puberty. Thus, the management of this disorder is challenging. DHT cream can improve prepubertal phallic growth in patients raised as male. Gonadectomy before adolescence and estrogen replacement at puberty can be considered in individuals raised as females who have a female gender identity. Disruption of alternative pathways to fetal DHT production might also present with 46,XY DSD (*AKR1C2/AKR1C4*).

Disorders of Androgen Action • ***ANDROGEN INSENSITIVITY SYNDROME*** Mutations in the androgen receptor cause resistance to androgen (testosterone, DHT) action or the *androgen insensitivity syndrome* (*AIS*). AIS is a spectrum of disorders that affects at least 1 in 100,000 46,XY individuals. Because the androgen receptor is X-linked, only 46,XY offspring are affected if the mother is a carrier of a mutation. XY individuals with *complete AIS* (formerly called *testicular feminization syndrome*) have a female phenotype, normal breast development