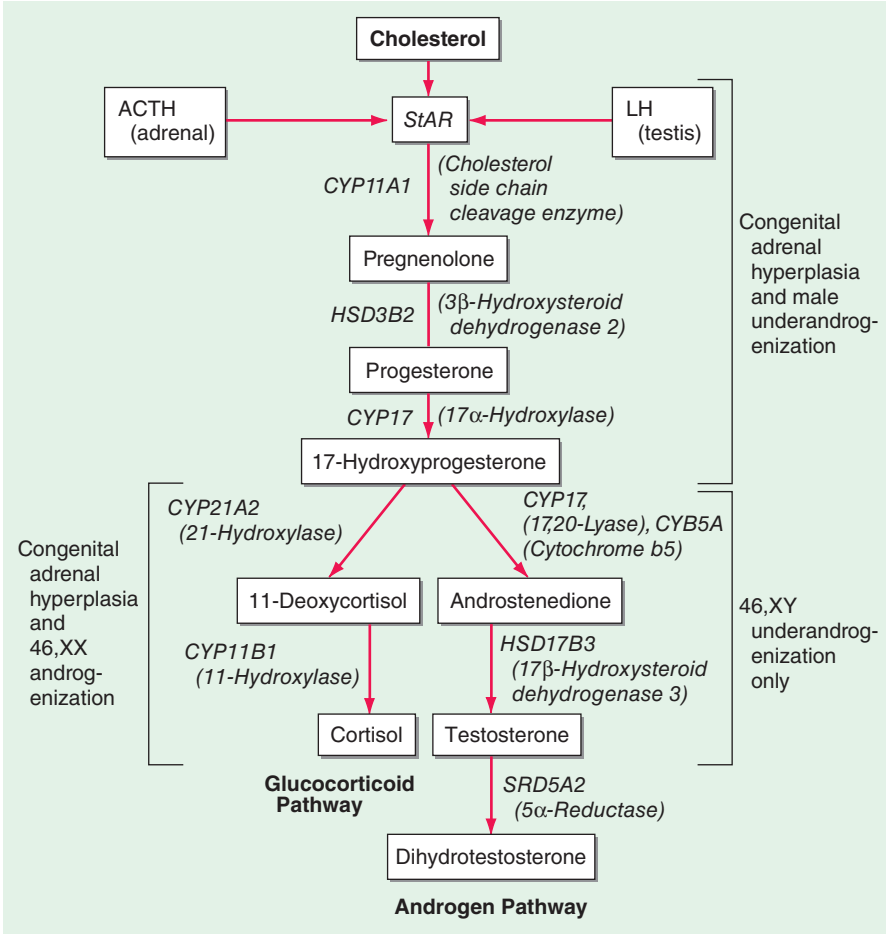

FIGURE 410-4 Simplified overview of glucocorticoid and androgen synthesis pathways. Defects in *CYP21A2* and *CYP11B1* shunt steroid precursors into the androgen pathway and cause androgenization of the 46,XX fetus. Testosterone is synthesized in the testicular Leydig cells and converted to dihydrotestosterone peripherally. Defects in enzymes involved in androgen synthesis result in underandrogenization of the 46,XY fetus. *StAR*, steroidogenic acute regulatory protein. *(After E Braunwald et al [eds]: Harrison's Principles of Internal Medicine, 15th ed. New York, McGraw-Hill, 2001.)*

Partial AIS (Reifenstein's syndrome) results from androgen receptor mutations that maintain residual function. Patients often present in infancy with penoscrotal hypospadias and small undescended testes and with gynecomastia at the time of puberty. Those individuals raised as males usually require hypospadias repair in childhood and may need breast reduction in adolescence. Some boys enter puberty spontaneously. High-dose testosterone has been given to support development if puberty does not progress, but long-term data are limited. More severely underandrogenized patients present with clitoral enlargement and labial fusion and may be raised as females. The surgical and psychosexual management of these patients is complex and requires active involvement of the parents and the patient during the appropriate stages of development. *Azoospermia* and male-factor infertility also have been described in association with mild loss-of-function mutations in the androgen receptor.

OTHER DISORDERS AFFECTING 46,XY MALES

Persistent müllerian duct syndrome is the presence of a uterus in an otherwise phenotypic male. This condition can result from mutations in AMH or its receptor (AMHR2). The uterus may be removed, but only if damage to the vasa deferentia and blood supply can be avoided. *Isolated hypospadias* occurs in ~1 in 250 males and is usually repaired surgically. Most cases are idiopathic, although evidence of penoscrotal hypospadias, poor phallic development, and/or bilateral cryptorchidism requires investigation for an underlying DSD (e.g., partial gonadal dysgenesis, mild defect in testosterone action, or even severe forms of 46,XX CAH). Unilateral undescended testes (cryptorchidism) affect more than 3% of boys at birth. Orchidopexy should be considered if the testis has not descended by 6–9 months of age. Bilateral cryptorchidism occurs less frequently and should raise suspicion of gonadotropin deficiency or DSD. A small subset of patients with cryptorchidism may have mutations in the insulin-like 3 (*INSL3*) gene or its receptor LGR8 (also known as *GREAT*), which mediates normal testicular descent. *Syndromic associations* and *intrauterine growth retardation* also occur relatively frequently in association with impaired testicular function or target tissue responsiveness, but the underlying etiology of many of these conditions is unknown.

46,XX DSD

Inappropriate androgenization of the 46,XX fetus (formerly called *female pseudohermaphroditism*) occurs when the gonad (ovary) contains androgen-secreting testicular material or after increased androgen exposure, which is usually adrenal in origin (Table 410-1).

46,XX Testicular/Ovotesticular DSD Testicular tissue can develop in 46,XX testicular DSD (46,XX males) after translocation of *SRY*, duplication of *SOX9*, or defects in *RSPO1* (Table 410-4).

Increased Androgen Exposure • *21-HYDROXYLASE DEFICIENCY (CONGENITAL ADRENAL HYPERPLASIA)* The *classic form* of 21-hydroxylase deficiency (21-OHD) is the most common cause of CAH (Chap. 406). It has an incidence between 1 in 10,000 and 1 in 15,000 and is the most common cause of androgenization in chromosomal 46,XX females (Table 410-4). Affected individuals are homozygous or compound heterozygous for severe mutations in the enzyme 21-hydroxylase (*CYP21A2*). This mutation causes a block in adrenal glucocorticoid and mineralocorticoid synthesis, increasing 17-hydroxyprogesterone and shunting steroid precursors into the androgen synthesis pathway (Fig. 410-4). Glucocorticoid insufficiency causes a compensatory elevation of adrenocorticotropin (ACTH), resulting in adrenal hyperplasia and additional synthesis of steroid precursors proximal to the enzymatic block. Increased androgen synthesis in utero causes androgenization of the 46,XX fetus in the first trimester. Ambiguous genitalia are seen at birth, with varying degrees of clitoral enlargement and labial fusion. Excess androgen production causes gonadotropin-independent precocious puberty in males with 21-OHD.

The *salt-wasting* form of 21-OHD results from severe combined glucocorticoid and mineralocorticoid deficiency. A salt-wasting crisis usually manifests between 5 and 21 days of life and is a potentially life-threatening event that requires urgent fluid resuscitation and steroid treatment. Thus, a diagnosis of 21-OHD should be considered in any baby with atypical genitalia with bilateral nonpalpable gonads. Males (46,XY) with 21-OHD have no genital abnormalities at birth but are equally susceptible to adrenal insufficiency and salt-losing crises.

Females with the *classic simple virilizing* form of 21-OHD also present with genital ambiguity. They have impaired cortisol biosynthesis but do not develop salt loss. Patients with *nonclassic 21-OHD* produce normal amounts of cortisol and aldosterone but at the expense of producing excess androgens. Hirsutism (60%), oligomenorrhea (50%), and acne (30%) are the most common presenting features. This is one of the most common recessive disorders in humans, with an incidence as high as 1 in 100 to 500 in many populations and 1 in 27 in Ashkenazi Jews of Eastern European origin.