TABLE 410-1 CLASSIFICATION OF DISORDERS OF SEX DEVELOPMENT (DSDS)

Sex Chromosome DSD	46,XY DSD (see Table 410-3)	46,XX DSD (see Table 410-4)
47,XXY (Klinefelter's syndrome and variants)	**Disorders of gonadal (testis) development**	**Disorders of gonadal (ovary) development**
45,X (Turner's syndrome and variants)	Complete or partial gonadal dysgenesis (e.g., SRY, SOX9, SF1, WT1, DHH, MAP3K1)	Gonadal dysgenesis
45,X/46,XY mosaicism (mixed gonadal dysgenesis)	Impaired fetal Leydig cell function (e.g., *SF1/NR5A1, CXorf6/MAMLD1*)	Ovotesticular DSD
46,XX/46,XY (chimerism/mosaicism)	Ovotesticular DSD	Testicular DSD (e.g., *SRY*+, dup *SOX9, RSPO1*)
	Testis regression	**Androgen excess**
	Disorders in androgen synthesis or action	Fetal
	Disorders of androgen biosynthesis	3β-Hydroxysteroid dehydrogenase II (*HSD3β2*)
	LH receptor (*LHCGR*)	21-Hydroxylase (*CYP21A2*)
	Smith-Lemli-Opitz syndrome	P450 oxidoreductase (*POR*)
	Steroidogenic acute regulatory (*StAR*) protein	11β-Hydroxylase (*CYP11B1*)
	Cholesterol side-chain cleavage (*CYP11A1*)	Glucocorticoid receptor mutations
	3β-Hydroxysteroid dehydrogenase II (*HSD3B2*)	Fetoplacental
	17α-Hydroxylase/17,20-lyase (*CYP17A1*)	Aromatase deficiency (*CYP19*)
	P450 oxidoreductase (*POR*)	Oxidoreductase deficiency (*POR*)
	Cytochrome b5 (*CYB5A*)	Maternal
	17β-Hydroxysteroid dehydrogenase III (*HSD17B3*)	Maternal virilizing tumors (e.g., luteomas)
	5α-Reductase II (*SRD5A2*)	Androgenic drugs
	Aldo-keto reductase 1C2 (*AKR1C2*)	**Other**
	Disorders of androgen action	Syndromic associations (e.g., cloacal anomalies)
	Androgen insensitivity syndrome	Müllerian agenesis/hypoplasia (e.g., MRKH)
	Drugs and environmental modulators	Uterine abnormalities (e.g., MODY5)
	Other	Vaginal atresia (e.g., McKusick-Kaufman)
	Syndromic associations of male genital development	Labial adhesions
	Persistent müllerian duct syndrome	
	Vanishing testis syndrome	
	Isolated hypospadias	
	Congenital hypogonadotropic hypogonadism	
	Cryptorchidism	
	Environmental influences	

Source: Modified from IA Hughes: Arch Dis Child 91:554, 2006.

fallopian tubes, uterus, and upper segment of the vagina. A female phenotype will develop in the absence of the gonad, but estrogen is needed for maturation of the uterus and breast at puberty.

DISORDERS OF CHROMOSOMAL SEX

Variations in sex chromosome number and structure can present as DSDs (e.g., 45,X/46,XY). KS (47,XXY) and TS (45,X) do not usually present with genital ambiguity but are associated with gonadal dysfunction (Table 410-2).

KLINEFELTER'S SYNDROME (47,XXY)

Pathophysiology The classic form of KS (47,XXY) occurs after meiotic nondisjunction of the sex chromosomes during gametogenesis (40% during spermatogenesis, 60% during oogenesis) (Chap. 83e). Mosaic forms of KS (46,XY/47,XXY) are thought to result from chromosomal mitotic nondisjunction within the zygote and occur in at least 10% of individuals with this condition. Other chromosomal variants of KS (e.g., 48,XXYY, 48,XXXY) have been reported but are less common.

Clinical Features KS is characterized by small testes, infertility, gynecomastia, tall stature/increased leg length, and hypogonadism in phenotypic males. It has an incidence of at least 1 in 1000 men, but approximately 75% of cases are not diagnosed. Of those who are diagnosed, only 10% are identified prepubertally, usually because of small genitalia or cryptorchidism. Others are diagnosed after puberty, usually based on impaired androgenization and/or gynecomastia. Developmental delay, speech difficulties, and poor motor skills may be features but are variable, especially in adolescence. Later in life, body habitus or infertility leads to the diagnosis. Testes are small and firm (median length 2.5 cm [4 mL volume]; almost always <3.5 cm [12 mL]) and typically seem inappropriately small for the degree of androgenization. Biopsies are not usually necessary but typically reveal seminiferous tubule hyalinization and azoospermia. Other clinical features of KS are listed in Table 410-2. Plasma concentrations of FSH and luteinizing hormone (LH) are increased in most adults with 47,XXY, and plasma testosterone is decreased (50–75%), reflecting primary gonadal failure. Estradiol is often increased, likely because of chronic Leydig cell stimulation by LH and aromatization of androstenedione by adipose tissue; the increased ratio of estradiol-to-testosterone results in gynecomastia (Chap. 411). Patients with mosaic forms of KS have less severe clinical features, have larger testes, and sometimes achieve spontaneous fertility.

TREATMENT KLINEFELTER'S SYNDROME

Growth, endocrine function, and bone mineralization should be monitored, especially from adolescence. Educational and psychological support is important for many individuals with KS. Androgen supplementation improves virilization, libido, energy, hypofibrinolysis, and bone mineralization in men with low testosterone levels but may occasionally worsen gynecomastia (Chap. 411). Gynecomastia can be treated by surgical reduction if it causes concern (Chap. 411). Fertility has been achieved by using in vitro fertilization in men with oligospermia or with intracytoplasmic sperm injection (ICSI) after retrieval of spermatozoa by testicular sperm extraction techniques. In specialized centers, successful spermatozoa retrieval using this technique is possible in >50% of men with nonmosaic