17 - 402 Sex Development

402 Sex Development

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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

TABLE 402-1 Classification of Differences (Disorders) of Sex Development (DSDs) SEX CHROMOSOME DSD 46,XY DSD (SEE TABLE 402-3) 46,XX DSD (SEE TABLE 402-4) 47,XXY (Klinefelter syndrome and variants) 45,X (Turner syndrome and variants) 45,X/46,XY mosaicism (mixed gonadal dysgenesis) 46,XX/46,XY (chimerism/mosaicism) Gonadal (testis) development Complete or partial gonadal dysgenesis Impaired fetal Leydig cell function Ovotesticular DSD Testis regression Disruption in androgen synthesis or action Disruption of androgen biosynthesis LH receptor (LHCGR) Smith-Lemli-Opitz syndrome (DHCR7) Steroidogenic acute regulatory (StAR) protein Cholesterol side-chain cleavage (CYP11A1) 3β-Hydroxysteroid dehydrogenase II (HSD3B2) 17α-Hydroxylase/17,20-lyase (CYP17A1) P450 oxidoreductase (POR) Cytochrome b5 (CYB5A) 17β-Hydroxysteroid dehydrogenase III (HSD17B3) 5α-Reductase II (SRD5A2) Aldo-keto reductase 1C2 (AKR1C2) Disruption of androgen action Androgen insensitivity syndrome Others include: Syndromic associations of male genital development Associated with fetal growth restriction Persistent müllerian duct syndrome Vanishing testis syndrome Isolated hypospadias Congenital hypogonadotropic hypogonadism Cryptorchidism Environmental influences Abbreviations: LH, luteinizing hormone; MODY, maturity-onset diabetes of the young; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome. Source: Reproduced with permission from IA Hughes et al: Consensus statement on management of intersex disorders. J Pediatr Urol 2:148, 2006. absence of the gonad, but estrogen is needed for maturation of the uterus and breast at puberty. The prenatal hormone environment is likely one of many factors influencing aspects of gender identity and behavior. This is an area of ongoing research and is beyond the scope of this chapter. DIFFERENCES 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 dys function (Table 402-3). TABLE 402-2 Presentation of Differences of Sex Development (DSD) at Different Stages of Life PRESENTATION FEATURES PROFESSIONAL EXAMPLES Prenatal Karyotype-phenotype discordance Obstetrician; fetal medicine Many Neonatal Atypical genitalia Obstetrician; neonatal medicine Many Salt-losing crisis Pediatrician CAH (CYP21A2) Childhood Hernia Surgeon CAIS Androgenization Endocrinologist CAH (CYP21A2, CYP11B1) Poor growth Pediatrician Turner, 45,X/46,XY Associated features Oncologist/nephrologist Wilms’ tumor Puberty Androgenization Estrogenization Absent puberty Endocrinologist Gonadal dysgenesis, CAH (CYP17A1), Turner Post-puberty Amenorrhea Gynecologist CAIS Adult Infertility Andrologist Klinefelter, 45,X/46,XY, SF1 Abbreviations: CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; 17β-HSD, 17β-hydroxysteroid dehydrogenase deficiency; SF1, steroidogenic factor 1 (NR5A1).

Gonadal (ovary) development Gonadal dysgenesis Ovotesticular DSD Testicular DSD Androgen excess Fetal 3β-Hydroxysteroid dehydrogenase II (HSD3B2) 21-Hydroxylase (CYP21A2) P450 oxidoreductase (POR) 11β-Hydroxylase (CYP11B1) Fetoplacental Aromatase deficiency (CYP19A1) Oxidoreductase deficiency (POR) Maternal Maternal virilizing tumors (e.g., luteomas) Androgenic drugs Others include: Syndromic associations (e.g., cloacal anomalies) Müllerian agenesis/hypoplasia (e.g., MRKH) Uterine abnormalities (e.g., MODY5) Vaginal atresia (e.g., McKusick-Kaufman) Labial adhesions Sex Development CHAPTER 402 ■ ■KLINEFELTER SYNDROME (47,XXY)

(SEE ALSO CHAP. 403) Pathophysiology The classic form of KS (47,XXY) occurs after meiotic nondisjunction of the sex chromosomes during gametogenesis (40% during spermatogenesis, 60% during oogenesis). Other forms of aneuploidy have similar features to KS (including mosaic 46,XY/47,XXY, 48,XXYY, and 48,XXXY) but are less common. KS has an incidence of at least 1 in 1000 men, but ~75% of cases are not diagnosed. Of those diagnosed, historically only 10% were identified prepubertally. How ever, noninvasive prenatal testing is leading to increased early detection. Endocrinologist Endocrinologist 17β-HSD, 5α-reductase, SF1 Ovotestis

WT1 Urogenital ridge SF1 SRY Bipotential gonad WNT4 RSPO1 FOXL2 46,XX 46,XY SOX9 Other genes Ovary Testis PART 12 Endocrinology and Metabolism Leydig cells Sertoli cells Granulosa cells AMH Testosterone DHT Müllerian regression Follicle development Male sexual differentiation FIGURE 402-2 The genetic regulation of gonadal development. See text for additional genes involved. AMH, anti-müllerian hormone (müllerian-inhibiting substance); DHT, dihydrotestosterone; FOXL2, forkhead transcription factor L2; RSPO1, R-spondin 1; SF1, steroidogenic factor 1 (also known as NR5A1); SOX9, SRYrelated HMG-box gene 9; SRY, sex-determining region on the Y chromosome; WNT4, wingless-type MMTV integration site 4; WT1, Wilms' tumor–related gene 1. Ovary Fallopian tube Uterus Vagina Female Male A Clitoris Labia minora Labia majora Vagina B Female Male FIGURE 402-3 Sex development. A. Internal urogenital tract. B. External genitalia.

Clinical Features KS is most commonly characterized by small testes, infertility, gynecomastia, tall stature/increased leg length, and hypogonadism in phenotypic males. At birth, most infants with KS do not have clinical features, although there are higher rates of cryptorchi dism and hypospadias. Most patients present in puberty with arrested pubertal development caused by testicular insufficiency. Others are diagnosed after puberty, based on low androgens, gynecomastia, or infertility. Testes are small and firm (median length 2.5 cm [4 mL volume]; almost always <3.5 cm [12 mL]) and typically seem inap propriately small for the degree of androgenization. Biopsies are not usually necessary but typically reveal seminiferous tubule hyaliniza tion and azoospermia. Other clinical features of KS are listed in Table 402-3. 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 insufficiency. Estra diol is often increased, resulting in gynecomastia (Chap. 403). Those with mosaic forms of KS have less severe clinical features, have larger testes, and sometimes achieve spontaneous fertility. TREATMENT Klinefelter Syndrome Growth, endocrine function, and bone mineralization should be monitored, especially from adolescence. Educational and psy chological support is important for many individuals with KS. Gonad Epididymis Mesonephros Mullerian duct .. Testis Wolffian duct Vas deferens Urogenital sinus Seminal vesicle Prostate Genital tubercle Genital swelling Urethral fold and groove Glans penis Shaft of penis Scrotum Penoscrotal raphe

TABLE 402-3 Possible Associated Clinical Features of Sex Chromosome Variations DISORDER COMMON CHROMOSOMAL COMPLEMENT GONAD Klinefelter syndrome 47,XXY or 46,XY/47,XXY Hyalinized testes Male Male Increased incidence of gynecomastia Small testes, azoospermia, decreased facial and axillary hair, decreased libido, tall stature and increased leg length, decreased penile length, increased risk of breast tumors, thromboembolic disease, learning difficulties, anxiety, speech delay and decreased verbal IQ, obesity, diabetes mellitus, metabolic syndrome, varicose veins, hypothyroidism, systemic lupus erythematosus, epilepsy Turner syndrome 45,X or 45,X/46,XX Streak gonad or immature ovary Clinical Features Infancy: lymphedema, web neck,

shield chest, low-set hairline, cardiac defects and coarctation of the aorta, urinary tract malformations, and horseshoe kidney Childhood: short stature, cubitus valgus, short neck, short fourth metacarpals, hypoplastic nails, micrognathia, scoliosis, otitis media and sensorineural hearing loss, ptosis and amblyopia, multiple nevi and keloid formation, autoimmune thyroid disease, visuospatial learning difficulties Adulthood: absent puberty and primary amenorrhea, hypertension, obesity, dyslipidemia, impaired glucose tolerance and insulin resistance, autoimmune thyroid disease, cardiovascular disease, aortic root dilation, osteoporosis, inflammatory bowel disease, chronic hepatic dysfunction, increased risk of colon cancer, hearing loss 45,X/46,XY mosaicism 45,X/46,XY Testis or streak gonad Variable Variable Usually male Short stature, increased risk of gonadal tumors, some Turner syndrome features Ovotesticular DSD 46,XX/46,XY Testis and ovary or ovotestis Clinical Features Possible increased risk of gonadal tumors Abbreviation: DSD, difference of sex development. Androgen supplementation improves virilization, libido, energy, hypofibrinolysis, and bone mineralization in men with low testos terone levels but may occasionally worsen gynecomastia (Chap. 403). Gynecomastia can be treated by surgical reduction if it causes concern (Chap. 403). 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 (Chap. 403). Long-term monitoring of men with KS is important given the increased risk of breast cancer, cardiovascular disease, metabolic syndrome, osteoporosis, and autoimmune disorders. Because most men with KS are never diagnosed, it is important that all internists consider this diagnosis in men with such features. ■ ■TURNER SYNDROME (GONADAL DYSGENESIS; 45,X) Pathophysiology TS is caused by complete or partial loss of one X chromosome and affects ~1 in 2500 women. Approximately one-half of women with TS have a 45,X karyotype, ~20% have 45,X/46,XX mosa icism, and the remainder have structural abnormalities of the X chro mosome, or Y chromosome material. The clinical features of TS likely result at least in part from haploinsufficiency of X chromosomal genes (especially in the pseudoautosomal region), but the exact mechanisms remain poorly understood. Clinical Features TS is characterized by female-typical external genitalia, short stature, hypergonadotropic hypogonadism, infertility, and other phenotypic features (Table 402-3). Infants may present with lymphedema, nuchal folds, low hairline, or left-sided cardiac defects or later in childhood with unexplained growth failure or delayed puberty. Although limited spontaneous pubertal development occurs in up to 30% of girls with TS (10%, 45,X; 60%, 45,X/46,XX) and up to 20% have menarche, the vast majority of women with TS develop complete ovarian insufficiency. Therefore, this diagnosis should be considered in all women who present with primary or secondary amenorrhea and elevated gonadotropin levels.

GENITALIA BREAST DEVELOPMENT EXTERNAL INTERNAL Clinical Features Sex Development CHAPTER 402 Female Hypoplastic female Immature female Clinical Features Variable Variable Gynecomastia TREATMENT Turner Syndrome The management of girls and women with TS requires a multi disciplinary approach to address many potentially affected organ systems according to TS practice guidelines. Individuals require long-term monitoring by an experienced cardiologist to follow con genital heart defects (CHDs) (30%) (bicuspid aortic valve, 30–50%; coarctation of the aorta, 30%; aortic root dilation, 5%), antibiotic prophylaxis for dental or surgical procedures, and serial magnetic resonance imaging (MRI) of aortic root dimensions, as progres sive aortic root dilation is associated with increased risk of aortic dissection. Individuals found to have congenital renal and urinary tract malformations (30%) are at risk for urinary tract infections, hypertension, and nephrocalcinosis. Hypertension can occur inde pendently of cardiac and renal malformations

and should be moni tored and treated as in other patients with essential hypertension. Regular assessment of thyroid function, weight, dentition, hearing, speech, vision, and educational issues should be performed during childhood. Counseling about long-term growth and fertility issues should be provided. Patient support groups are active throughout the world and can play an invaluable role. Short stature is common, and untreated final height rarely exceeds 150 cm in nonmosaic 45,X TS. Recombinant growth hormone is used to increase adult height. Girls with evidence of ovarian insufficiency require estrogen replacement to induce breast and uterine development, support growth, and maintain bone mineralization. Most physicians now initiate low-dose estrogen therapy to induce puberty at an age-appropriate time (~11 years). Doses of estrogen are increased gradually to allow development over a 2- to 4-year period. Progestins are added later to regulate withdrawal bleeds. A very small percentage of women with TS have had spontaneous pregnancy, whereas others have achieved success ful pregnancy after ovum donation and in vitro fertilization, but the risks of cardiac complications are high, and expert counseling and

management are needed. The existence of Y chromosome mate rial in individuals with TS increases the risk for germ cell tumors, and gonadectomy has traditionally been advised. Increasingly, it is recommended that this decision also weigh potential for gonadal function and the importance of autonomous decision-making. Long-term follow-up of women with TS includes careful surveil lance of sex hormone replacement and reproductive function, bone mineralization, cardiac function and aortic root dimensions, blood pressure, weight and glucose tolerance, hepatic and lipid profiles, thyroid function, celiac disease screening, skin examination, and hearing. This service is provided by a dedicated TS clinic in some centers.

PART 12 Endocrinology and Metabolism ■ ■45,X/46,XY MOSAICISM The phenotype of individuals with 45,X/46,XY mosaicism (sometimes called mixed gonadal dysgenesis) can vary considerably. Some have a predominantly female phenotype (see TS above). Most 45,X/46,XY individuals have a male phenotype and testes, and the diagnosis is made incidentally after amniocentesis or during investigation of infertility. In practice, most newborns referred for assessment have atypical genitalia and variable somatic features. There is often marked asymmetry, with a streak gonad and hemiuterus on one side and a partially descended dysgenetic testis and hemiscrotum on the other side. Many children are raised as boys, but in some children, sex desig nation (whether to raise the baby as male or female) must be decided by parents and the multidisciplinary team. There is an increased risk of germ cell cancer (GCC), up to 35% in intraabdominal gonads, so prophylactic removal of intraabdominal gonads is usually consid ered. Individuals raised as males often have hypospadias surgery 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 (and possibly biopsy) at the time of puberty. Testosterone supplementation may be required in puberty or adulthood if low testosterone is detected. Potential associated features (e.g., cardiac, renal) should be monitored according to TS guidelines. Infertility is typical, but non-azoospermia or focal spermatogenesis has been reported, highlighting the impor tance of individualized approaches to management. ■ ■OVOTESTICULAR DSD Ovotesticular DSD (OTDSD) is a condition in which an individual has both ovarian and testicular tissue, either by having both an ovary and a testis or by having an ovotestis. Most individuals with this diagnosis have a 46,XX karyotype (especially in individuals of African ancestry), although 46,XX/46,XY chimerism and very rarely a 46,XY karyotype is also possible. OTDSD usually presents with atypical genitalia at birth and sometimes breast development, cyclical hematuria, and/or phallic

development at puberty. Progressive regression of the ovarian and/or testicular component can occur over time. Gender identity varies in OTDSD but often aligns with assigned sex. Risk of GCC is also elevated in OTDSD (~3%). Infertility is typical (especially in 46,XX testes with no Y chromosome), but births have occurred via ovum or sperm from individuals with other forms of OTDSD. DIFFERENCES OF GONADAL AND PHENOTYPIC SEX Differences of gonadal and phenotypic sex can result in reduced andro gen production or action in individuals with a 46,XY karyotype (46,XY DSD) or excess androgen production in individuals with a 46,XX karyotype (46,XX DSD) (Table 402-1). These conditions cover a spec trum of phenotypes ranging from phenotypic females with a Y chro mosome to phenotypic males with a 46,XX karyotype to individuals with atypical genitalia. Karyotype is a useful starting investigation for diagnosis with basic biochemical profiling. High-throughput genetic testing can help in reaching a definitive diagnosis. ■ ■46,XY DSD Underandrogenization of the 46,XY fetus reflects defects in andro gen production or action. It can result from disruption of testis

development, defects of androgen synthesis, or resistance to testoster one and DHT (Table 402-1). Disruption of Testis Development • TESTICULAR DYSGENESIS

Complete gonadal dysgenesis (CGD, Swyer’s syndrome) is associated with streak gonads, müllerian structures (due to insufficient AMH/ MIS secretion), and a complete absence of androgenization. Pheno typic females with this condition usually 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. Individuals with CGD typically identify as female. The risk of GCC is high, and intraabdominal gonads should be removed. In con trast, patients with partial gonadal dysgenesis (PGD, dysgenetic testes) may produce enough MIS to regress the uterus and sufficient testoster one for partial androgenization and, therefore, usually present in the newborn period with atypical genitalia, highlighting the spectrum of features that are typically seen with many DSDs. Testicular dysgenesis can result from disruption of testis-promoting genes (e.g., WT1, SF1, SRY, SOX9, MAP3K1, DHH, DHX37, and oth ers) or, rarely, duplication of chromosomal loci containing “antitestis” genes (e.g., DAX1) (Table 402-4). Among these, deletions or mutations of SRY and heterozygous mutations of SF1 (NR5A1) or DHX37 appear to be most common but still account collectively for <30% of cases. Associated clinical features may be present (Table 402-4). A family history of DSD, hypospadias, infertility, or early menopause is impor tant because variations in some genes (e.g., SF1/NR5A1, SOX8) can be associated with a range of reproductive phenotypes. SF1 variants are sometimes inherited from a mother in a sex-limited dominant man ner (which can mimic X-linked inheritance), and a woman may later develop primary ovarian insufficiency because of the effect of SF1 on the ovary. Gender identity can be variable in PGD. Dysgenetic testes have an increased risk of GCC. For descended testes, monitoring via physical examination is appropriate. If testes are intraabdominal and not able to be brought down, they may be removed to prevent GCC (risk up to 35% if intraabdominal). Dysgenetic testes may or may not produce sufficient testosterone for puberty. In those who identify as male, testosterone replacement may be needed. In those who identify as female, estrogen replacement will be needed for female-typical pubertal development and ongoing sex steroid requirements. Absent (vanishing) testis syndrome (bilateral anorchia) reflects regression of the testis during development. The absence of müllerian structures indi cates adequate secretion of AMH early in utero. Usually, androgeniza tion of the external genitalia is normal. The etiology is often unknown but sometimes associated with pathogenic variants in DHX37. These individuals can be offered testicular

prostheses and androgen replace ment in adolescence and typically identify as male. Disruption of Androgen Synthesis Defects in the pathway that regulates androgen synthesis (Fig. 402-4) cause underandrogenization of the 46,XY fetus (Table 402-1). Müllerian regression is unaffected because Sertoli cell function is preserved, and no uterus is found. These conditions can present with a spectrum of genital appearances, ranging from female-typical external genitalia or clitoromegaly in some individuals to penoscrotal hypospadias or a small phallus in others. LH RECEPTOR Pathogenic variants in the LH receptor (LHCGR) cause Leydig cell hypoplasia and testosterone insufficiency due to LH resistance. STEROIDOGENIC ENZYME PATHWAYS Mutations in steroidogenic acute regulatory protein (StAR) and CYP11A1 affect both adrenal and gonadal steroidogenesis (Fig. 402-4) (Chap. 398). Affected individuals (46,XY) usually have severe early-onset salt-losing adrenal failure and a female phenotype, although later-onset milder variants are increasingly reported. Defects in 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) also cause adrenal insufficiency in severe cases, but the accumula tion of dehydroepiandrosterone (DHEA) has a mild androgenizing effect, resulting in atypical genitalia or hypospadias. Salt loss occurs in many but not all children. Patients with CAH due to 17α-hydroxylase (CYP17A1) deficiency have variable underandrogenization and develop hypertension and hypokalemia due to the potent salt-retaining effects

TABLE 402-4 Selected Genetic Causes of 46,XY Differences of Sex Development (DSDs) GENE INHERITANCE GONAD UTERUS EXTERNAL GENITALIA ASSOCIATED FEATURES Disruption of Testis Development WT1 AD Dysgenetic testis +/– Female or ambiguous Wilms' tumor, renal abnormalities, gonadal tumors (WAGR, DenysDrash and Frasier syndromes) SF1/NR5A1 AR/AD (SL) Dysgenetic testis/ Leydig dysfunction +/– Female, ambiguous or male SRY Y Dysgenetic testis or ovotestis +/– Female or ambiguous SOX9 AD Dysgenetic testis or ovotestis +/– Female or ambiguous Campomelic dysplasia DHX37 AD Dysgenetic testis +/– Female, ambiguous or male Other causes of testicular dysgenesis include: DMRT1, CBX2, MAP3K1, SOX8, ZNRF3, GATA4/ZFPM2 (congenital heart disease), DHH (neuropathy), ARX (X-linked lissencephaly), TSPYL1 (sudden infant death), MYRF (diaphragmatic hernia), ESR2/NR3A2, SAMD9 (MIRAGE syndrome), ATRX (blood), PPP1R12A (brain, gastrointestinal), MAMLD1, dupXp21, dup1p35, del9p24, del10q23, and in several other congenital syndromes Disruption of Androgen Synthesis LHCGR AR Testis – Female, ambiguous or micropenis DHCR7 AR Testis – Variable Smith-Lemli-Opitz syndrome: coarse facies, second-third toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities STAR AR Testis – Female or ambiguous Congenital lipoid adrenal hyperplasia (primary adrenal insufficiency) CYP11A1 AR Testis – Female or ambiguous Primary adrenal insufficiency HSD3B2 AR Testis – Ambiguous CAH, primary adrenal insufficiency ± salt loss, partial androgenization due to ↑ DHEA CYP17A1 AR Testis – Female or ambiguous CAH, hypertension due to ↑ corticosterone and 11-deoxycorticosterone, except in isolated 17,20-lyase deficiency CYB5A AR Testis – Ambiguous Apparent isolated 17,20-lyase deficiency; methemoglobinemia POR AR Testis – Ambiguous or male Mixed features of 21-hydroxylase deficiency and 17α-hydroxylase/17,20-lyase deficiency, sometimes associated with Antley-Bixler craniosynostosis HSD17B3 AR Testis – Female or ambiguous Partial androgenization at puberty, ↑ androstenedione-to-testosterone ratio SRD5A2 AR Testis – Ambiguous or micropenis AKR1C2 (AKR1C4) AR Testis – Female or ambiguous Decreased fetal DHT production Disruption of Androgen Action Androgen receptor X Testis – Female, ambiguous, micropenis or normal male Abbreviations: AD, autosomal dominant; AKR1C2, aldo-keto reductase family 1 member 2; AR, autosomal recessive; ARX, aristaless related homeobox, X-linked; CAH, congenital adrenal hyperplasia; CBX2, chromobox

homologue 2; CYB5A, cytochrome b5; CYP11A1, P450 cholesterol side-chain cleavage; CYP17A1, cytochrome P450 family 17 subfamily A member 1; DAX1, dosage sensitive sex-reversal, adrenal hypoplasia congenita on the X chromosome, gene 1; DHEA, dehydroepiandrosterone; DHCR7, sterol 7 δ reductase; DHH, desert hedgehog; DMRT1,doublesex and mab3-related transcription factor 1; GATA4, GATA binding protein 4; HSD17B3, 17β-hydroxysteroid dehydrogenase type 3; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; LHR, LH receptor; MAP3K1, mitogen-activated protein kinase kinase kinase 1; MIRAGE, myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MYRF, myelin regulatory factor; POR, P450 oxidoreductase; SF1, steroidogenic factor 1; SL, sex-limited; SOX8, SRY-related HMG-box gene 8; SOX9, SRY-related HMG-box gene 9; SRD5A2, 5α-reductase type 2; SRY, sex-related gene on the Y chromosome; StAR, steroidogenic acute regulatory protein; TSPYL1, testis-specific Y-encoded-like protein 1; WAGR, Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation; WNT4, wingless-type mouse mammary tumor virus integration site, 4; WT1, Wilms' tumor–related gene 1; ZFPM2, zinc finger protein, multitype 2; ZNRF3, zinc and ring finger 3. of corticosterone and 11-deoxycorticosterone. Patients with complete loss of 17α-hydroxylase function often present as phenotypic females who do not enter puberty and are found to have inguinal testes and hypertension in adolescence. Some mutations in CYP17A1 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 reduced androgen production and a biochemical pattern of apparent combined 21-hydroxylase and 17α-hydroxylase deficiency, sometimes with skeletal abnormalities (Antley-Bixler cra niosynostosis). Defects in 17β-hydroxysteroid dehydrogenase type 3 (HSD17B3) 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

Primary adrenal failure (rare); hyposplenia (common); primary ovarian insufficiency in female (46,XX) relatives Sex Development CHAPTER 402 Testicular regression syndrome Leydig cell hypoplasia Partial androgenization at puberty, ↑ testosterone-todihydrotestosterone ratio Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia and infertility phallic development can occur during adolescence due to the action of other enzyme isoforms. Individuals with 5α-reductase type 2 defi ciency have normal wolffian structures and usually do not develop sig nificant breast tissue. At puberty, the increase in testosterone may lead to virilizing features despite DHT deficiency. DHT gel can improve prepubertal phallic growth in patients raised as male. Prevention of testosterone exposure (by gonadectomy or pubertal suppression) in adolescence and estrogen replacement at puberty can be considered in individuals who identify as female. Disruption of alternative path ways to fetal DHT production might also present with 46,XY DSD (AKR1C2/AKR1C4). Disruption of Androgen Action • ANDROGEN INSENSITIV ITY SYNDROME Pathogenic variants 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

Cholesterol LH (testis) ACTH (adrenal) StAR (Cholesterol side chain cleavage enzyme) CYP11A1 Pregnenolone (3β-hydroxysteroid dehydrogenase 2) HSD3B2 PART 12 Endocrinology and Metabolism Progesterone (17α-hydroxylase) CYP17A1 17-hydroxyprogesterone CYP17A1, (17,20-

lyase), CYB5A (Cytochrome b5) CYP21A2 (21-hydroxylase) Congenital adrenal hyperplasia and 46,XX androg- enization 11-deoxycortisol Androstenedione HSD17B3 (17β-hydroxysteroid dehydrogenase 3) CYP11B1 (11-hydroxylase) Cortisol Testosterone Glucocorticoid Pathway SRD5A2 (5α-reductase) Dihydrotestosterone Androgen Pathway FIGURE 402-4 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. ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; StAR, steroidogenic acute regulatory protein. at least 1 in 100,000 46,XY individuals. Because the androgen receptor is X-linked, only 46,XY offspring are affected. The condition is usually inherited from a mother who carries the sequence variant but can also arise de novo. XY individuals with complete AIS (formerly called tes ticular feminization syndrome) have a female phenotype, normal breast development (due to aromatization of testosterone), a short vagina but no uterus (because AMH/MIS production is normal), sometimes scanty pubic and axillary hair, and typically a female gender identity and sex role behavior. Gonadotropins can be variable, but testoster one is usually elevated and AMH/MIS levels in childhood are normal or high. CAIS sometimes presents as inguinal hernias (containing testes) in childhood or more often with primary amenorrhea in late adolescence. In the past, gonadectomy was recommended early in childhood. Increasingly, risk of tumor development is weighed against potential for endogenous hormone function. Thus gonadectomy is often delayed and gonads are left in situ until breast development is complete. Subsequently, the adolescent or young adult should be coun seled about the risk of malignancy and the option for gonadectomy (with estrogen replacement), especially because early detection of pre malignant changes by imaging or biomarkers is currently not possible. The use of graded dilators in adolescence or young adulthood is often sufficient to dilate the vagina for sexual activity. Partial AIS (Reifenstein’s syndrome) results from androgen recep tor mutations that maintain residual function. Patients often present in infancy with penoscrotal hypospadias and undescended testes and with gynecomastia at the time of puberty. Gender identity can be vari able. At puberty, testes produce testosterone with variable phenotypic development. For those who identify as male, high-dose testosterone has been given to support development if puberty does not progress,

but long-term data are limited. For those raised as female, testosterone effects at puberty can be prevented (by pubertal suppression) and femaletypical puberty induced with estrogen. They also have an increased risk of GCC, again raising the question of if and when to perform gonadec tomy. Azoospermia and male-factor infertility also have been described in association with mild loss-of-function mutations in the androgen receptor. Androgen resistance without AR vari ants is called type 2 AIS (e.g., DAAM2). Congenital adrenal hyperplasia and 46,XY underandrog- enization ■ ■OTHER DISORDERS AFFECTING 46,XY MALES Persistent müllerian duct syndrome is the pres ence of a uterus in an otherwise phenotypic male. This condition can result from pathogenic variants in AMH or its receptor (AMHR2). Isolated hypospadias occurs in ~1 in 250 males. Many less severe cases are idiopathic. However, evidence of penoscrotal hypospadias, poor phal lic development, bilateral cryptorchidism, and/ or other clinical features requires investigation for an underlying DSD (e.g., partial gonadal dysgenesis, partial defect in testosterone action, or even severe forms of 46,XX CAH) or one of many DSD/hypospadias-associated syndromes. Unilateral undescended testes (cryptorchidism) affect >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. 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 except in specific syndromes (e.g., MIRAGE [myelodys plasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy], IMAGe [intrauter ine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genitourinary abnormalities]). 46,XY underandrog- enization only ■ ■46,XX DSD Androgenization (virilization) of the 46,XX fetus occurs when the gonad (ovary) contains androgen-secreting testicular tissue or after increased androgen exposure, which is usually adrenal in origin (Table 402-1). 46,XX Testicular DSD Testicular tissue can develop in 46,XX tes ticular DSD (46,XX males) most often following translocation of SRY. This may be diagnosed with karyotype/phenotype discordance or later in life during evaluation for hypogonadism or infertility. Individuals with this condition develop testes with normal testosterone produc tion, leading to external male phenotype in utero, and produce AMH/ MIS to regress müllerian structures. They have azoospermia due to lack of the AZF region of the Y chromosome. Progressive testicular regression and hypogonadism are common. Gender identity is typi cally male. 46,XX OTDSD Ovotestes (or testes) can also develop in individu als with a 46,XX karyotype following upregulation of SOX9 or SOX3 or defects in RSPO1, NR2F2, WT1, or SF1/NR5A1 (Table 402-5). OTDSD is discussed above under “Differences of Chromosomal Sex.” 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. 398), and it is the most common cause of androgeniza tion in chromosomal 46,XX children (incidence around 1 in 15,000

TABLE 402-5 Selected Genetic Causes of 46,XX Differences of Sex Development (DSDs) GENE INHERITANCE GONAD UTERUS EXTERNAL GENITALIA ASSOCIATED FEATURES Testicular/Ovotesticular DSD SRY Translocation Testis or ovotestis – Male or ambiguous SF1/NR5A1 (codon 92) AD Testis or ovotestis +/– Male or ambiguous Other causes of testicular/ovotesticular DSD include: COUP-TF2/NR2F2 (congenital heart disease), RSPO1 (palmar plantar hyperkeratosis, squamous cell skin carcinoma), WNT4 (SERKAL syndrome), WT1 (in zinc finger 4), dysregulation/duplication of SOX3 (Xq27) and SOX9 (dup17q24) Increased Androgen Synthesis HSD3B2 AR Ovary + Clitoromegaly CAH, primary adrenal insufficiency, mild androgenization due to ↑ DHEA CYP21A2 AR Ovary + Ambiguous CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal insufficiency to simple virilizing forms with compensated adrenal function, ↑ 17-hydroxyprogesterone POR AR Ovary + Ambiguous or female Mixed features of 21-hydroxylase deficiency and 17α-hydroxylase/17,20-lyase deficiency, sometimes associated with Antley-Bixler craniosynostosis CYP11B1 AR Ovary + Ambiguous CAH, hypertension due to ↑ 11-deoxycorticosterone CYP19 AR Ovary + Ambiguous Maternal virilization during pregnancy, absent breast development at puberty Abbreviations: ACTH, adrenocorticotropin; AD, autosomal dominant; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; COUP-TF2, chicken ovalbumin upstream promoter transcription factor 2; CYP11B1, 11β-hydroxylase; CYP19, aromatase; CYP21A2, 21-hydroxylase; DHEA, dehydroepiandrosterone; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; POR, P450 oxidoreductase; RSPO1, R-spondin 1; SERKAL, sex reversion, kidneys, adrenal and lung dysgenesis; SF1, steroidogenic factor 1; SOX3, SRY-related HMG-box gene 3; SOX9, SRY-related HMG-box gene 9; SRY, sex-related gene on the Y chromosome; WT1, Wilms’ tumor–related gene 1. live births) (Table 402-5). Affected individuals are

homozygous or compound heterozygous for severely disruptive sequence variants in the gene (CYP21A2) encoding the enzyme 21-hydroxylase. Impaired 21-hydroxylase activity prevents adrenal glucocorticoid and mineralo corticoid synthesis, thus shunting steroid precursors into the androgen synthesis pathway (Fig. 402-4). Increased androgen synthesis in utero causes androgenization of the 46,XX fetus in the first trimester. Atypi cal genitalia are usually seen at birth, with varying degrees of clitoral enlargement and labial fusion. 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 insuf ficiency and salt-losing crises. Excess androgen production can cause gonadotropin-independent precocious puberty in males with 21-OHD. Nonclassic 21-OHD is discussed in Chap. 398. TREATMENT Congenital Adrenal Hyperplasia Acute salt-wasting crises require fluid resuscitation, IV hydro cortisone, and correction of hypoglycemia. Once the patient is stabilized, glucocorticoids must be given to correct the cortisol insufficiency and suppress adrenocorticotropic hormone (ACTH) stimulation, thereby preventing further virilization, rapid skeletal maturation, and the development of polycystic ovaries. Mineralo corticoid replacement may be needed. Salt supplements may be required in early life. In childhood, treatment is also titrated care fully to prevent impairment of linear growth. In the future, different forms of glucocorticoid replacement and multimodal therapies may improve treatment options. See Chap. 398 for detailed discussion of hormone replacement. Individuals with 46,XX CAH due to classic 21-OHD historically often underwent genitoplasty in infancy, but if and when these procedures should be performed is debated. Concerns have arisen about the importance of assent/consent by the individual for genital surgery, potential long-term side effects related to sexual function and ability to achieve orgasm, and the increased incidence of non female gender identity. Surgical options include vaginoplasty and clitoroplasty. When vaginoplasty is performed in infancy, surgical

 revision or vaginal dilation may still be needed in adolescence or adulthood and, if deferred, may be necessary for menstrual flow or intercourse. Current clinical practice guidelines can vary in different countries, including supporting parents to defer sur gery or for individuals to have no surgery. Women with 21-OHD frequently develop polycystic ovaries and have subfertility. The latter occurs due to multiple factors including anatomic barriers, hormone imbalances, and psychological effects of the condition. Preconception genetic counseling is recommended. Due to con cerns about fetal neurologic development, prenatal treatment with dexamethasone to prevent androgenization of a fetus is currently not recommended unless in a study protocol that allows long-term follow-up of all children treated. The treatment of other forms of CAH (including in 46,XY indi viduals) includes mineralocorticoid and glucocorticoid replace ment for salt-losing conditions (e.g., StAR, CYP11A1, HSD3B2), suppression of ACTH drive with glucocorticoids in disorders asso ciated with hypertension (e.g., CYP11B1), and appropriate sex hor mone replacement in adolescence and adulthood, when necessary. OTHER CAUSES Increased androgen synthesis can also occur in CAH due to defects in POR, 11β-hydroxylase (CYP11B1), and 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) and with mutations in the genes encoding aromatase (CYP19A1). Increased androgen exposure in utero can occur with maternal virilizing tumors, luteomas, and ingestion of androgenic compounds. ■ ■OTHER DISORDERS AFFECTING 46,XX FEMALES Congenital absence of the vagina occurs in association with müllerian agenesis or hypoplasia as part of the Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. This diagnosis should be considered in otherwise phenotypic females with primary amenorrhea. Associated features

include renal (agenesis) and cervical spinal abnormalities. ■ ■LONG-TERM FOLLOW-UP Whether a DSD is diagnosed during childhood or adulthood, many individuals will require ongoing care. Medical care may include hor mone replacement, optimization of bone health, screening related to other associated clinical features, and care for infertility or sterility. There is increasing attention to fertility preservation and investiga tional gonadal tissue cryopreservation in the pediatric and young adult population, which may allow for increased fertility potential in adulthood. More frequently, individuals retain gonadal tissue at

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