Sex Development

Part 12: Endocrinology and Metabolism

KEY CLINICAL POINTS

1. Sex development involves three distinct components: chromosomal sex, gonadal sex (determination), and phenotypic sex (differentiation).
2. Approximately 1 in 5000 newborns require investigation for atypical or ambiguous genitalia.
3. Klinefelter syndrome (47,XXY) occurs in at least 1 in 1000 men, but ~75% remain undiagnosed.
4. Turner syndrome (45,X) affects ~1 in 2500 women; presence of Y chromosome material increases germ cell tumor risk.
5. Androgen Insensitivity Syndrome (AIS) is X-linked and only affects 46,XY individuals.
6. Salt-losing crisis is a life-threatening presentation associated with Congenital Adrenal Hyperplasia (CAH).
7. Steroidogenesis pathway: Defects in CYP21A2 or CYP11B1 lead to androgenization of 46,XX fetuses; defects in CYP17A1, CYB5A, HSD17B3, or SRD5A2 lead to 46,XY androgens insufficiency.
8. Karyotype is the primary starting investigation for diagnosing sex development disorders (DSD).
9. Gonadectomy is traditionally advised for Turner syndrome patients with Y chromosome material due to tumor risk.
10. Recombinant growth hormone is used to increase adult height in Turner syndrome.

DEFINITION & CLASSIFICATION

- **Development Timeline:** Begins in utero and continues into young adulthood until sexual maturity/reproductive capability.
- **Three Components of Development:**
- **Chromosomal sex:** Defined by karyotype (e.g., 46,XY; 46,XX) established at fertilization.
- **Gonadal sex:** Histologic and functional characteristics of gonadal tissue (testis or ovary).
- **Phenotypic sex:** Structure of external/internal genitalia and secondary sex characteristics.
- **Terminology:** 'Intersex' and 'hermaphrodite' replaced by 'disorder of sex development' (DSD) or 'ovotesticular DSD'.
- **Care Approach:** Multidisciplinary team required (medical, psychosocial, urogynecologic).

EPIDEMIOLOGY

- **Atypical/Ambiguous Genitalia:** ~1 in 5000 babies.
- **Klinefelter Syndrome (KS):** ≥ 1 in 1000 men; ~75% are not diagnosed.
- **Turner Syndrome (TS):** ~1 in 2500 women.
- 45,X karyotype: ~1 in 2500 women.
- 45,X/46,XX mosaicism: ~20% of TS cases.

- **Hypospadias:** ~1 in 250 males.
- **Cryptorchidism:** >3% of boys at birth.

ETIOLOGY & PATHOPHYSIOLOGY

Genetic Regulation of Gonadal Development

- **SRY (Sex-determining region on the Y chromosome):** Initiates testis development from ~42 days post-conception.
- **SOX9:** Regulated by SRY; leads to a cascade of genes for testis development.
- **Ovarian Development:** Not passive; involves genes like WNT4 and RSPO1 (may repress testis development).
- **Key Genes:** FOXL2, WT1, SF1 (NR5A1), DAX1.

Androgen Synthesis Pathways

- **Steroidogenesis Pathway (Figure 402-4):**
- Cholesterol → Pregnenolone (via **CYP11A1**)
- Pregnenolone → Progesterone (via **HSD3B2**)
- Progesterone → 17-hydroxyprogesterone (via **CYP17A1**)
- 17-hydroxyprogesterone → 11-deoxycortisol (via **CYP21A2**) → Cortisol (via **CYP11B1**)
- 17-hydroxyprogesterone → Androstenedione (via **CYP17A1, CYB5A**)
- Androstenedione → Testosterone (via **HSD17B3**)
- Testosterone → Dihydrotestosterone (via **SRD5A2**)
- **Clinical Consequences of Pathway Defects:**
- **CYP21A2 / CYP11B1 defects:** Shunt precursors to androgen pathway → androgens in 46,XX fetuses.
- **CYP17A1 / CYB5A / HSD17B3 / SRD5A2 defects:** Result in underandrogenization of 46,XY fetuses.

CLINICAL FEATURES

Presentation by Life Stage (Table 402-2)

- **Prenatal:** Karyotype-phenotype discordance, atypical genitalia.
- **Neonatal:** Salt-losing crisis (CAH), hernia (CAH), androgenization (CAH).
- **Childhood:** Poor growth (Turner, 45,X/46,XY), associated features (Wilms' tumor).
- **Puberty:** Androgenization (17β-HSD, 5α-reductase, SF1), Estrogenization (Ovotestis), Absent puberty (Gonadal dysgenesis, CAH, Turner).
- **Post-puberty:** Amenorrhea (CAIS).
- **Adult:** Infertility (Klinefelter, 45,X/46,XY, SF1).

Specific Disorders (Table 402-3)

- **Klinefelter Syndrome (47,XXY):**
- **Genitalia:** Male; **Gonad:** Hyalinized testes.
- **Features:** Small testes, azoospermia, gynecomastia, tall stature, increased leg length, decreased libido/facial hair, risk of breast tumors, metabolic syndrome, and cardiovascular disease.

- **45,X/46,XY Mosaicism:** Short stature, high risk of gonadal tumors, some TS features.
- **Ovotesticular DSD:** Variable genitalia; potential increased risk of gonadal tumors.
- **Turner Syndrome (45,X):**
- **Genitalia:** Female; **Gonad:** Streak gonad or immature ovary.
- **Infancy:** Lymphedema, web neck, shield chest, cardiac defects (coarctation of aorta), horseshoe kidney.
- **Childhood:** Short stature, cubitus valgus, scoliosis, hearing loss, visuospatial learning difficulties.
- **Adulthood:** Primary amenorrhea, hypertension, obesity, aortic root dilation, osteoporosis.

DIFFERENTIAL DIAGNOSIS

- **Diagnostic Strategy:** Karyotype is the starting investigation; high-throughput genetic testing provides definitive diagnosis.
- **Classification of 46,XY DSDs (Table 402-4):**
- **Disruption of Testis Development:** WT1 (Wilms' tumor), SF1/NR5A1 (adrenal failure), SRY, SOX9, DHX37.
- **Disruption of Androgen Synthesis:** LHCR, DHCR7 (Smith-Lemli-Opitz), STAR (CAH), CYP11A1, HSD3B2 (CAH), CYP17A1 (CAH/hypertension), CYB5A, POR, HSD17B3, SRD5A2, AKR1C2.
- **Disruption of Androgen Action:** Androgen receptor (AIS spectrum).
- **Classification of 46,XX DSDs (Table 402-5/6):**
- **Testicular/Ovotesticular DSD:** SRY, SF1, RSPO1, WNT4.
- **Increased Androgen Synthesis:** HSD3B2, CYP21A2, CYP11B1 (CAH variants).

DIAGNOSTIC APPROACH

1. **Initial Assessment:** Evaluate for atypical genitalia, absent puberty, or primary amenorrhea.
2. **Karyotype Analysis:** Determine chromosomal complement (46,XX, 46,XY, mosaicism).
3. **Hormonal Profiling:** Measure FSH, LH, Testosterone, Estradiol, AMH/MIS, Inhibin B.
   - *Note:* In complete gonadal dysgenesis, FSH/LH are elevated; testosterone is decreased (50-75%); estradiol may be increased (causing gynecomastia).
4. **Genetic Testing:** High-throughput sequencing for specific genes (SRY, SOX9, CYP21A2, etc.).
5. **Imaging:** Ultrasound or MRI of gonads and internal structures (uterus, ovaries, kidneys).
6. **Cardiac Evaluation:** Echocardiogram for Turner syndrome (coarctation, bicuspid aortic valve).
7. **Tumor Surveillance:** Regular examination for germ cell tumors in individuals with Y chromosome material.

MANAGEMENT & TREATMENT

1. **Monitoring:**
   - Track growth, endocrine function, and bone mineralization from adolescence.
   - Monitor thyroid function, weight, dentition, hearing, speech, vision, and education.
   - For Turner: Cardiac follow-up (aortic root dimensions) and metabolic health (glucose/lipids).
2. **Support:**

- Provide educational and psychological support; utilize patient support groups.

3. **Hormone Replacement Therapy:**
   - **Estrogen:** Start at age ~11 for Turner syndrome to induce breast/uterine development and maintain bone mineral density (gradual increase over 2-4 years).
   - **Progestins:** Added later in Turner syndrome to regulate withdrawal bleeds.
   - **Testosterone:** For men with low levels to improve virilization, libido, energy, and bone mineralization.
   - **Growth Hormone:** Recombinant GH for height increase in Turner syndrome.
4. **Surgical & Procedural Management:**
   - **Gonadectomy:** Traditionally advised for Turner syndrome if Y chromosome material exists (due to tumor risk).
   - **Genitoplasty:** Controversial; performed for infants/young children prior to age of consent.
   - **Hypospadias Surgery:** For individuals raised as males.
   - **Removal of Dysgenetic Gonads:** If gonads cannot be brought down into the scrotum.
   - **Testicular Prostheses:** Offered to individuals with Ovotesticular DSD.

PROGNOSIS & COMPLICATIONS

- **Klinefelter Syndrome (KS):** Risk of breast cancer, cardiovascular disease, metabolic syndrome, osteoporosis, and autoimmune disorders.
- **Turner Syndrome (TS):** Risk of germ cell tumors, congenital heart defects (30%), coarctation of the aorta (30%), aortic root dilation (5%), hypertension, and osteoporosis.
- **45,X/46,XY Mosaicism:** High risk of gonadal tumors (up to 35% in intraabdominal gonads).
- **Ovotesticular DSD:** Increased risk of gonadal tumors (~3%).
- **Androgen Insensitivity Syndrome (AIS):** Increased risk of germ cell tumors.
- **Persistent Müllerian Duct Syndrome:** Presence of a uterus in an otherwise phenotypic male.

KEY PEARLS & HIGH-YIELD POINTS

- **Y Chromosome Risk:** Presence of Y chromosome material in Turner syndrome → increased risk for germ cell tumors → traditional recommendation for gonadectomy.
- **CAH Warning:** Salt-losing crisis is a life-threatening presentation associated with congenital adrenal hyperplasia (CAH).
- **Diagnostic Entry Point:** Karyotype is the essential first step in investigation for DSD.
- **Fertility Management:** ICSI or sperm extraction from testicular tissue can be used for men with oligospermia/Klinefelter syndrome.

REFERENCE TABLES

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	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

TABLE 402-2

Presentation of Differences of Sex Development (DSD) at Different Stages of Life PRESENTATION Prenatal Neonatal...

PRESENTATION	FEATURES	PROFESSIONAL	EXAMPLES
Prenatal	Karyotype-phenotype discordance	Obstetrician; fetal medicine	Many
	Atypical genitalia Salt-losing crisis	Obstetrician; neonatal medicine Pediatrician	
	Hernia Androgenization Poor growth Associated features	Surgeon Endocrinologist Pediatrician Oncologist/nephrologist	

PRESENTATION	FEATURES	PROFESSIONAL	EXAMPLES
Puberty	Androgenization Estrogenization	Endocrinologist Endocrinologist	17β-HSD, 5α-reductase, SF1 Ovotestis
	Absent puberty	Endocrinologist	Gonadal dysgenesis, CAH (CYP17A1), Turner
	Amenorrhea	Gynecologist	
Adult	Infertility	Andrologist	Klinefelter, 45,X/46,XY, SF1

TABLE 402-3

Possible Associated Clinical Features of Sex Chromosome Variations DISORDER Klinefelter syndrome

DISORDER	COMMON CHROMOSOMAL COMPLEMENT	GONAD	GENITALIA		BREAST DEVELOPMENT
			EXTERNAL	INTERNAL	
Klinefelter syndrome	47,XXY or 46,XY/47,XXY	Hyalinized testes	Male	Male	Increased incidence of gynecomastia
	Clinical Features				
Turner syndrome	45,X or 45,X/46,XX	Streak gonad or immature ovary	Female	Hypoplastic female	Immature female
	Clinical Features				
	Infancy: lymphedema, webneck, shield chest, low-set hairline, cardiac defects and coarctation of the aorta, urinary tract malformations, and horseshoe kidney				

DISORDER	COMMON CHROMOSOMAL COMPLEMENT	GONAD	GENITALIA	BREAST DEVELOPMENT
	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			

DISORDER	COMMON CHROMOSOMAL COMPLEMENT	GONAD	GENITALIA		BREAST DEVELOPMENT
	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
	Clinical Features				
Ovotesticular DSD	46,XX/46,XY	Testis and ovary or ovotestis	Variable	Variable	Gynecomastia
	Clinical Features				
	Possible increased risk of gonadal tumors				

TABLE 402-4

Selected Genetic Causes of 46,XY Differences of Sex Development (DSDs) GENE Disruption of Testis Development WT1

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, Denys-Drash and Frasier syndromes)
SF1/NR5A1	AR/AD (SL)	Dysgenetic testis/ Leydig dysfunction	+/–	Female, ambiguous or male	Primary adrenal failure (rare); hyposplenia (common); primary ovarian insufficiency in female (46,XX) relatives
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	Testicular regression syndrome
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					

GENE	INHERITANCE	GONAD	UTERUS	EXTERNAL GENITALIA	ASSOCIATED FEATURES
AR	Testis	–	Female, ambiguous or micropenis		
AR	Testis	–			
AR	Testis	–			
AR	Testis	–			
AR	Testis	–	Variable		
AR	Testis	–	Female or ambiguous		
AR	Testis	–			
AR	Testis	–	Female or ambiguous		
AR	Testis	–			
AR	Testis	–	Ambiguous		
AR	Testis	–	Female or ambiguous		
			Ambiguous		
			Ambiguous or male		
			Female or ambiguous		
			Ambiguous or micropenis		
			Female or ambiguous		
Disruption of Androgen Action					
Androgen receptor	X	Testis	–	Female, ambiguous, micropenis or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia and infertility

TABLE 402-5

Selected Genetic Causes of 46,XX Differences of Sex Development (DSDs) GENE Testicular/Ovotesticular

GENE	INHERITANCE	GONAD	UTERUS	EXTERNAL GENITALIA	ASSOCIATED FEATURES
Testicular/Ovotesticular DSD					
SRY	Translocation	Testis or ovotestis	–	Male or ambiguous	

GENE	INHERITANCE	GONAD	UTERUS	EXTERNAL GENITALIA	ASSOCIATED FEATURES
	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					
	AR	Ovary	+	Clitoromegaly	
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
	AR	Ovary	+	Ambiguous or female	
CYP11B1	AR	Ovary	+	Ambiguous	CAH, hypertension due to ↑ 11-deoxycorticosterone
	AR	Ovary	+	Ambiguous	