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Sexual Differentiation and Disorders of Sex Development

Al Hassani N[1] and Souid A[2]*

[1]Department of Pediatrics, Tawam Hospital, Alain City, United Arab Emirates

[2]Department of Pediatrics, College of Medicine and Health Sciences - UAE University, Alain City, United Arab Emirates

Abbreviations

TDF: Testis Determining Factor; SOX9: SRY-Box 9; SRY: Sex Region on the short arm of Y chromosome

Sexual Differentiation (Sex Development and Maturation)

Sexual differentiation refers to the processes through which a male or female phenotype develops. It typically follows the sex determination as embryonic gonads become testes or ovaries. The sex chromosome complement XY differentiates indifferent (primitive) gonads into testes, whereas the XX differentiates them into ovaries [1,2]. The developing gonads then drive the differentiation of the internal genitalia from a double system (Wolffian and Müllerian) and the external genitalia from a single system (urogenital sinus and genital [phallic] tubercle), as summarized in the adjoining Schema.

The SRY gene (sex-determining region Y [MIM#480000]) on the short arm of the Y chromosome (Yp11.2) is responsible for the development of testes (productions of testosterone and anti-Mullerian hormone). Absence of SRY gene in the sex chromosome complement XX leads to the formation of ovaries. Thus, sexual development in the female embryo requires only lack of SRY. Two X chromosomes, however are needed for the full development of females as evident by the incomplete female phenotype in Turner syndrome (XO genotype).

SRY is responsible for the male development (maleness). This gene encodes the transcription factor Testis Determining Factor (TDF) that activates SOX9 (SRY-Box 9; MIM#608160) which encodes a transcription factor that drives sex determination and skeletal development. TDF binds to an upstream enhancer sequence of SOX9; expressions of TDF and SOX9 are essential for testicular development in male embryos.

Testis determining factor plus SOX9 stimulate Sertoli cells to produce anti-Mullerian hormone and interstitial (Leydig) cells to produce testosterone. In male embryos, the anti-Mullerian hormone blocks female development (the Mullerian system). Testosterone on the other hand differentiates the Wolffian system into epididymis, vas deferens, seminal vesicles and ejaculatory ducts. Testosterone also differentiates the urogenital sinus into posterior urethra, prostate gland and bulbo-urethral glands of Cowper. In the presence of dihydrotestosterone (synthesized from testosterone by 5-α reductase), the genital (phallic) tubercle develops into the glans penis, the urethral folds develop into the corpus spongiosum (enclosing the urethra) and the labio-scrotal folds fuse to form the scrotum and ventral part of the penis (Figure 1) [3].

In female embryos the absence of anti-Mullerian hormone results in involution of the Wolffian system, while the Müllerian system develops into Fallopian tubes, uterus and upper third of the vagina. In the absence of testosterone, the urogenital sinus develops into the lower two-thirds of the vagina, urethra, paraurethral glands of Skene and vestibular glands of Bartholin. In the absence of dihydrotestosterone, the genital (phallic) tubercle develops into clitoris, the urethral folds develop into labia minora, and the labio-scrotal folds develop into labia majora (Figure 1).

Schema

Sexually indifferent stage = Primitive gonads + Mullerian duct + Wolffian duct

Female – XX (no SRY)

Primitive gonads → Ovaries

The Mullerian system → Fallopian tubes + uterus + upper third of vagina

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Correspondence:
Noura Ali Rashed Ali Al Hassani, Consultant Physician, Endocrinology (PEDS Diabetic C - Medical Affairs), Tawam Hospital, 15258, Al Ain, United Arab Emirates.
Tel: +971 37677444
E-mail: nohassani@seha.ae

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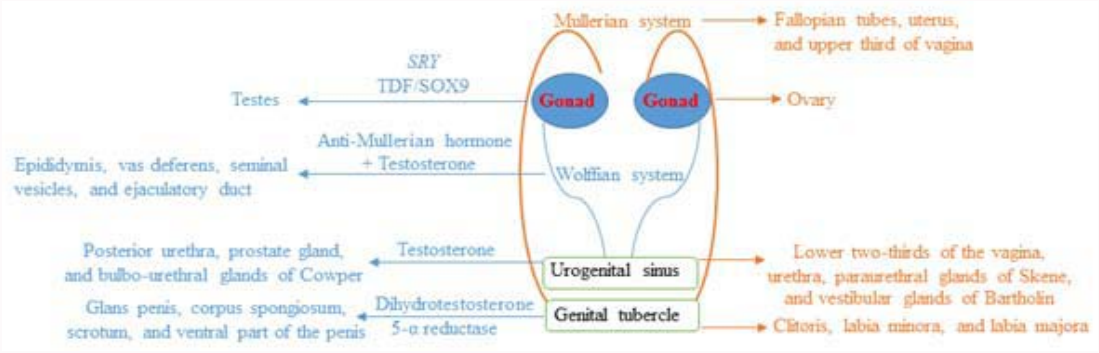

Figure 1: Left: Differentiation of the male internal genital tracts from the Wolffian system and external genitalia from the single system (urogenital sinus and genital tubercle). Right: Differentiation of the female internal genital tracts from the Mullerian system and external genitalia from the single system (urogenital sinus and genital tubercle).

Table 1: 46, XY DSD' (Sex Reversed XY).

Androgen (testosterone) insensitivity (X-linked inheritance, MIM#300068)	***46,XY sex reversal 1' [SRXY1], MIM#400044 (SRY mutation, non-functional SRY)***
XY with female external genitalia + primary amenorrhea XY (*SRY* present) → ↑Testis determining factor + ↑SOX9 → (1) ↑Anti-Mullerian hormone → Blocking the Mullerian system → No fallopian tubes, uterus, and upper vagina (only a blind lower vaginal pouch) + (2) ↑Testosterone + androgen receptor defect (insensitivity) → No testicular and Wolffian system (no maleness, 'unfinished male', 'under-virilized') 'Testosterone is required for the formation of testes and male genitalia'.	XY with female internal and external genitalia + primary amenorrhea XY (*SRY* absent) → Only one X (similar to Turner syndrome) → Indifferent gonads (gonadal dysgenesis), as the full XX complement is required for the formation of ovaries. (1) Absence of anti-Mullerian hormone → Complete female genitalia (Fallopian tubes, uterus, and upper vagina). (2) Absence of testosterone → No testicular and Wolffian duct development (no maleness).
Of note: Embryonic life starts with the genital organ '*phallus*', which develops into a penis or clitoris. The presence of normal scrotum and palpable testes indicates a male karyotype.	

Genitalia → Lower two third of the vagina

Two X chromosomes are needed for the full development of female phenotype, which explains the incomplete female in the XO genotype of Turner syndrome.

Male - XY (SRY)

SRY → ↑Testis Determining Factor (TDF) → ↑SOX9

'TDF/SOX9' → Primitive gonads → Testes → ↑Testosterone → Testicular development + promotes Wolffian system → Male genitalia (testes, penis, and scrotum)

Testes → ↑anti-Mullerian hormone → Blocks the Mullerian duct system

The testosterone produced by fetal testes determines maleness.

Ambiguous Genitalia

The term genital ambiguity describes the difficulty in determining the gender of a newborn because of: (1) small scrotal sacs that look like enlarged labia (Figure 2), (2) no palpable testes, (3) microphallus that looks like hypospadia or enlarged clitoris (Figure 3) or (4) no obvious vaginal opening.

Physical examination reliably determines whether the gonads are palpable. Palpable gonads in the scrotum imply the presence of the Y chromosome material SRY, which leads to testicular formation. The examination also estimates the degree of virilization.

Different levels of virilization of the external genitalia have been graded (I to V) using the staging system of Prader [4]. Stage I is a normal female external genitalia with a slightly enlarged clitoris and a slightly reduced vaginal opening. Stage II is an abnormal appearing genitalia with a middle-size phallus, a small vaginal opening (with a separate urethral opening), and a posterior labial fusion. Stage III is an enlarged phallus with a single urogenital sinus and a complete fusion of the labia. Stage IV is male genitalia with an empty scrotum and a phallus of the size of a normal penis but adhered to the perineum. Stage V is a complete male virilization with a normal penis, a urethral opening at or near the tip a normal scrotum but empty, and normal ovaries and uterus; the vagina connects internally with the urethra [5].

Penile growth is linear with time during mid-to-late gestation:

Penile length (cm) = -2.27 + (0.16 x weeks' gestation).

The term 'microphallus' ('micropenis') describes a 'stretched penile length' of <2.5 SD below the mean, which is a function of the gestational age, weight and height. The mean ± SD stretched penile length in a full-term newborn is 3.5 ± 0.4cm. Thus measurements <2.5cm warrant evaluation [5,6,7].

Patients with ambiguous genitalia require evaluation and counseling for Disorders of Sex Development (DSD). The work-up includes serum testosterone (elevated in SRY expression), serum adrenal androgens (elevated in congenital adrenal hyperplasia), and pelvic ultrasonography. The decision regarding gender of rearing is made by the parents after multidisciplinary evaluations to assist them in making the most informed decision possible. Considerations when determining gender of rearing include genetic sex, underlying diagnosis, internal and external anatomy, urologic or sexual function, response to testosterone, surgical outcome, and likelihood of gender identity. Ethical principles that apply to this situation include autonomy (the right for individuals to make their own decisions), beneficence (the benefit to the patient), and nonmaleficence (avoiding harm) [8,9].

Disorders of Sex Development (DSD)

The term 'disorders of sex development' refers to conditions with

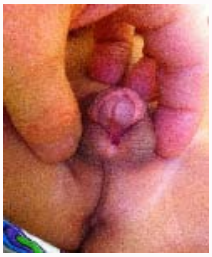

Figure 2:

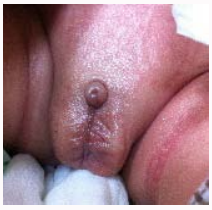

Figure 3:

atypical gonads or gender phenotype. It is classified into three main groups based on the karyotype: (1) 46, XY DSD, (2) 46, XX DSD and (3) sex chromosomal DSD [10].

'46, XY DSD' refers to disorders of testicular development (conditions that block male development, 'sex-reversed XY'). Complete types are associated with streak gonads, Mullerian structures (fallopian tubes, uterus, and upper vagina), and female external genitalia. Partial types are associated with ambiguous genitalia and impaired development of the Wolffian system (epididymis, vas deferens, seminal vesicle, and ejaculatory duct). Causes of '46,XY DSD' include: (1) disorders of androgen synthesis (e.g., 5-α reductase deficiency), (2) disorders of androgen action (e.g., complete or partial androgen insensitivity due to pathologic variants involving the androgen receptor gene on Xq12 [MIM#313700]), (3) disorders of gonadal (testicular) development (e.g., SRY pathologic variants, 46,XY sex reversal 1' [SRXY1], MIM#400044) and (4) others entities including persistent Mullerian duct syndrome [11]. Table 1 summarizes the differences between androgen insensitivity and SRY mutation.

Androgen insensitivity is the most common cause of '46, XY DSD'. Incomplete expression of androgen receptor mutations (partial androgen insensitivity, MIM#312300) may cause mild clitromegaly, true ambiguous genitalia, hypospadias alone or impaired fertility in otherwise normal XY phenotype. Complete expression of androgen receptor mutations (MIM#300068) on the other hand causes whole female phenotype (blind vaginal pouch without Mullerian structures) and infertility. Mutations in the androgen receptor gene (MIM#313700) may also cause hypospadia 1, X-linked disease (MIM#300633).

Example of partial androgen insensitivity: A newborn has a stretched phallus length of 1.0cm (normal stretch length at birth ≥2.5cm). The urethral meatus is visible at the base (no hypospadia). There is a bifid scrotum. The gonads are palpable in the scrotum. Family history is positive for maternal aunts who are infertile (complete androgen insensitivity).

The term '46, XX DSD' (sex-reversed XX) describes conditions that block female development, such as disorders of gonadal (ovary) development or androgen excess. Congenital Adrenal Hyperplasia (CAH) is the most common cause of 46, XX DSD. Deficiency of 21 hydroxylase is most common type of CAH and results in deficiencies of both glucocorticoids and mineralocorticoids with excess of androgens. It presents clinically with life-threatening salt crisis in both the XX & XY genotype while ambiguous genitalia in only XX genotype. Virilization (clitoromegaly and fused perineum) and hypertension (accumulation of deoxycorticosterone and 11-deoxycorstisol) suggest 11-beta-hydroxylase deficiency, where renin and aldosterone are suppressed. Palpable testes in the scrotum in a newborn with ambiguous genitalia exclude 21-hydroxylase or 11-hydroxylase deficiency.

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