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Review Article

Sex assignment and Re-assignment: A pediatric endocrinologist perspective; more than three decades of experience

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Abstract: The birth of a child with disorder in sex development (DSD) poses a major psychological impact on the family and involves a specialized and experienced multi-disciplinary team to work with the family. There has been progress in diagnosis, surgical techniques and understanding psychosocial issues related to the management. The issue of sex assignment is so complex and challenging. This review reflects a pediatric endocrinologist perspective which developed over more than thirty years of experience.
Keywords: sex, assignment, reassignment, perspective, endocrinologist.

INTRODUCTION

Disorders of sex development (DSD), formerly termed intersex condition, atypical genitalia, or ambiguous genitalia, constitutes a complex major social and medical emergency, figures 1 and 2. It can result from so many causes, of which, congenital adrenal hyperplasia (CAH) accounts for the majority. Several forms of congenital adrenal hyperplasia results in significant salt-loss, which if unrecognized and not appropriately treated may lead to shock [1-3]. The Lawson Wilkin Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) published suggested changes to the previously known nomenclature, (table 1) [4-7].

Table 1: Revised nomenclature

Previous	Proposed
Intersex	Disorders of sex development (DSD)
Male pseudo hermaphrodite (under virilization of an XY male, under masculinization of an XY male)	46, XY DSD
Female pseudo hermaphrodite (over virilization of an XX female, masculinization of an XX female)	46, XX DSD
True hermaphrodite	Ovotesticular DSD
XX male (XX sex reversal)	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

Physicians who care for a child who have DSD must understand the embryology and physiology of sexual differentiation, and appreciate the cultural, religious and psychological needs and avoid determining sex of rearing before accurate diagnosis is reached [8-9]. In this review, we will discuss the embryology and physiology of sexual differentiation, causes, diagnosis, clinical approach to ambiguous genitalia and its management.

Embryology and physiology of sexual differentiation

The H-Y antigen, a minor male-specific histocompatibility antigen located on the long arm of the Y chromosome, was widely believed to be the primary testis-inducer. However, recent studies have implicated several genes on the short arm of the Y chromosome, including the gene known as sex-determining region Y (SRY), in the development of the testis and in the determination of male gender. The gene for the anti-müllerian hormone (AMH) has been elucidated, and a reliable assay for its measurement has been developed [10-15]. The gene that codes for the androgen receptor has also been identified, furthering our understanding of complete and partial androgen-resistance syndromes [16] In addition, the genetic marker that results in 5-α-reductase deficiency has

recently been identified, [17] and this discovery extends our understanding of the actions of testosterone and dihydro testosterone (DHT). Another important research project shows that the female pathway is not simply a default pathway and that several genes actively regulate female development [18]. The processes of sex determination and differentiation proceed in sequence, as shown in Figure 3.

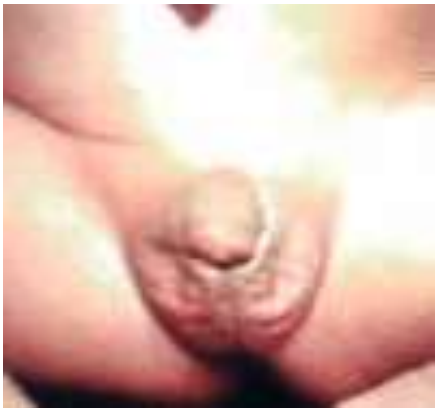

Fig 1: shows Ambiguous genitalia in a 46 XX patients diagnosed with congenital adrenal hyperplasia due to 21-α-hydroxylase deficiency.
Note: The complete masculination with normal looking hyper pigmented male genitalia, but with no palpable gonads.

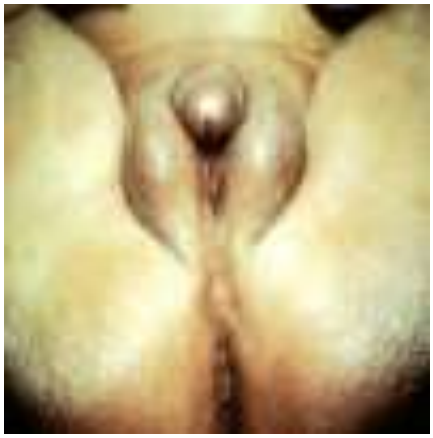

Fig 2: Ambiguous genitalia in 46 XY patients diagnosed with congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase deficiency.
Note, the pigmented short, curved phallus, central urogenital slit and separated labioscrotal testicle.

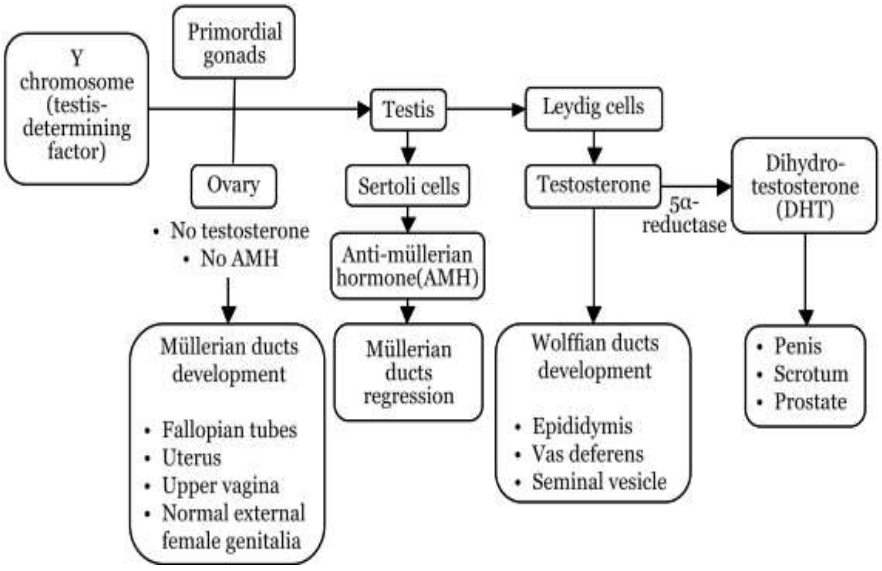

Fig 3: Simplified model for sexual differentiation and the development of internal and external genitalia.

Genetically, sex is determined fertilization, by the contribution of a Y or an X chromosome from the sperm; this contribution determines the differentiation of the primordial gonads. Thus, the presence or absence of a Y chromosome, with its testis-determining factor, primarily determines the course of sexual differentiation. This differentiation is visible by the 4th week of gestation; the XY karyotype is normally associated with male differentiation, and the XX karyotype is normally associated with female development. Complete female sexual differentiation occurs in the absence of the male determinant, but female differentiation is probably regulated by a specific genetic pathway that originates on the long arm of the X chromosome.

The presence of a single Y chromosome, even in the presence of more than one X chromosome, is sufficient to cause the development of a testis. Testicular differentiation to produce functional Leydig and Sertoli cells occurs by the 7th week of gestation and is a rapid phenomenon. This rapid differentiation contrasts with the slower development of the ovaries in the 20th week of gestation. At 7thweek, the Sertoli cells are actively secreting AMH and Leydig cells are secreting testosterone, and this secretion is controlled

by placental human chorionic gonadotrophin (hCG). Thereafter, the foetal pituitary gland controls testicular function in the 2nd and 3rd trimesters. Undifferentiated embryos possess two internal duct systems, müllerian (paramesonephric) ducts and wolffian (mesonephric) ducts, but the differentiation of the internal and external genitalia is essentially complete by the end of the 1st trimester. The presence of testosterone and AMH protects the genetically male foetus from inadvertent feminization [19].

Locally secreted testosterone promotes the development of the ipsilateral wolffian duct into the epididymis, vas deferens, ejaculatory duct, and seminal vesicle. Testosterone production by one testis has no effect on the wolffian duct development on the opposite side. AMH produced by the Sertoli cells causes regression of the ipsilateral müllerian duct. Similar to the local control of the wolffian duct, müllerian duct regression is dependent on the local secretion of AMH and unaffected by AMH secretion from the contra lateral testis. [20,21] Thus, differences in the secretion of testosterone or AMH by the two gonads can result in the presence of male internal ducts on one side and female structures on the other side. As male internal duct differentiation requires high local concentrations of testosterone, a virilised female with ovaries still has normal female internal structures. Exposure of female foetuses to androgen in early gestation, before 12th week, can lead to variable degrees of virilisation (Prader's classification), as shown in Table 2; however, labioscrotal fusion cannot be achieved after 12th week [22, 23].

Table-2: Degree of virilisation of the external genitalia according to Prader's classification (23)

Classification	Characteristics
Type 1 (P-1)	Clitoral hypertrophy
Type 2 (P-2)	Clitoral hypertrophy, urethral and vaginal orifices present, but very near
Type 3 (P-3)	Clitoral hypertrophy, single urogenital orifice, posterior fusion of the labia majora
Type 4 (P-4)	Penile clitoris, perioneoscrotal hypospadias, complete fusion of the labia majora
Type 5 (P-5)	Complete masculinisation (normal-looking male genitalia) but no palpable testes

The lack of AMH, as well as insensitivity to AMH, is known to yield persistent müllerian duct syndrome. A recent study reports that males with a 46,XY karyotype can be characterized by the presence of Fallopian tubes and a uterus; the external genitalia of these XY individuals are male, and testicular function is otherwise normal [21].

Traditionally, the appearance of the external genitalia indicates the appropriate gender assignment. Male development depends on adequate testosterone secretion, peripheral metabolism of testosterone to dihydrotestosterone (DHT), and peripheral tissue response to androgens. Male external genitalia differentiate in response to DHT, which is formed in genital skin and other sensitive structures by the metabolism of testosterone by the 5-α-reductase enzyme. The presence of DHT induces the elongation of the genital tubercle, fusion of the genital folds to form the penis, fusion of the labioscrotal folds to form the scrotum, and the formation of the prostate. The response of these structures to DHT requires the presence of a normal intracellular androgen receptor. The formation of the male external genitalia is complete by the end of the 1st trimester. After the 1st trimester, further development consists only of growth of the penis and the descent of the testes into the scrotum. Both of these developments depend on the levels of foetal pituitary gonadotrophin. In the normal female, the external genitalia do not differentiate into male-specific anatomy; the genital tubercle remains small and becomes the clitoris, and the genital and labioscrotal folds remain unfused to form the labia minora and labia majora, respectively [24-32].

Table-3:Major causes of disorders of sex development (DSD) according to karyotype

46,XX Karyotype		
46,XX DSD	• Congenital adrenal hyperplasia (CAH)	• Enzyme deficiency ▪ 21α-hydroxylase ▪ 11β-hydroxylase ▪ 3β-hydroxysteroid Dehydrogenase
	• Ovarian/adrenal tumours (mother–child)	
	• Exposure to exogenous medication (synthetic progestin preparation)	
Ovotesticular DSD		

46,XY Karyotype		
46,XY DSD	• Lack of synthesis of testosterone	• Testicular differentiation ▪ pure gonadal dysgenesis ▪ absence of Leydig cells or luteinising hormone receptor ▪ testicular regression ▪ gonadotrophin hormone deficiency • Enzyme deficiency in testosterone pathway ▪ 20,22-desmolase ▪ 17,20-lyase ▪ 3β-hydroxysteroid dehydrogenase ▪ 17α-ketoreductase
	• Lack of synthesis of dihydrotestosterone	• 5α-reductase deficiency
	• End-organ-unresponsiveness (resistance)	• Partial • Complete
Ovotesticular DSD		
Multiple or local congenital anomalies		
Mixed Karyotype		
Ovotesticular DSD 46,XX/46,XY		
Mixed gonadal dysgenesis 45,X/46,XY		

Major causes of disorders of sex development (DSD):

It is important to understand the physiology and embryology of sex-determination and sexual differentiation, but it is also essential to know the different causes of DSD; these causes are shown in Table 3. Most patients are known to have either 46,XX DSD or 46,XY DSD conditions. In 46,XX DSD individuals (previously known as female-pseudo hermaphrodites), normal ovaries and internal female organs are present; however, there are variable degrees of virilisation of the external genitalia among different individuals. Congenital adrenal hyperplasia, due to a deficiency in the 21α-hydroxylase enzyme or due to deficiencies in the 11β-hydroxylase and 3-β-hydroxysteroid dehydrogenase enzymes, constitutes the majority of DSD cases [33-43]. Congenital adrenal hyperplasia is not an uncommon autosomal recessive condition; it is prevalent in the Arab population due to a high rate of consanguineous matings [44] Saedi-Wong et al.; [45] reported a high prevalence of consanguineous mating among the Saudi Arabian population. However, 46,XY DSD individuals (previously known as male pseudo hermaphrodites) develop normal testes but with incomplete virilisation(under-masculinised external male genitalia, due to a variety of causes.

Only a small portion of patients have genital ambiguities extensive enough to make the determination of sex-of-rearing difficult. Ovotesticular DSD individuals (previously known as true hermaphrodites) are rare; both testicular and ovarian tissues are present in these individuals. The most common karyotypes in ovotesticular DSD cases is 46,XX, but karyotypes of 46,XY or 46,XX/46,XY can also lead to ovotesticular DSD. The appearance of the internal and external genitalia is variable in individuals with ovotesticular DSD, and the assignment of sex for ovotesticular DSD cases usually depends on the amount of functional testicular tissue. Other disorders of gonadal differentiation, such as pure or mixed-gonadal dysgenesia or testicular regression, should be considered potential causes of ambiguous genitalia, and the presence or absence of these gonadal disorders should be investigated at the time of diagnosis. The diagnosis of ambiguous genitalia can be made only by laparoscopy or by a combination of laparotomy and a histological examination of the gonads [46-48] Ambiguous genitalia in genetic males may be comprised of multiple malformation syndromes, such as Smith-Lemli-Opitz, Vater, and Meckel's syndromes [49-50].

Thus, the presence of other morphogenic anomalies usually indicates a non-endocrine explanation for the abnormal appearance of the genitalia. Furthermore, local ano-rectal and uro-genital anomalies such as epispdius and bladder extrophy are

known to be associated with external genital ambiguity [50].

Diagnostic approach:

The initial assessment of a DSD patient requires a detailed maternal and family history, as well as a careful physical examination for symptoms including hyper pigmentation, signs of salt-wasting; and anal or other local or generalized dysmorphology. The initial assessment should also provide documentation of the existing external genitalia.

Proper genital examination at birth and before declaring the sex of a child is always encouraged to prevent the trauma of sex reassignment later in life. Children with ambiguous genitalia should be transferred immediately to a facility where specialized physicians are available. A multidisciplinary team consisting of a paediatric endocrinologist, paediatric surgeon, urologist, plastic surgeon, geneticist, and a psychologist or paediatric psychiatrist should collaborate in managing such a condition. The trauma associated with gender assignment is less when the sex-of-rearing is determined by an expert as soon as possible after birth as opposed to the experience of a gender re-assignment later in life [8, 9, 47, and 51].

A logical work-up in a child with ambiguous genitalia include the following:

- chromosomal analysis
- serum chemistry including serum glucose and electrolyte
- appropriate hormonal studies, and specification
- genetic studies

Radiological studies:

Pelvic ultrasonography can be performed initially which allows visualization of a neonate's adrenal glands, which may be enlarged in congenital adrenal hyperplasia (CAH), however, normal adrenal glands in ultrasonography do not exclude congenital adrenal hyperplasia, when adrenal glands are enlarged in patients with CAH, they have a cribriform appearance (Figure 4).

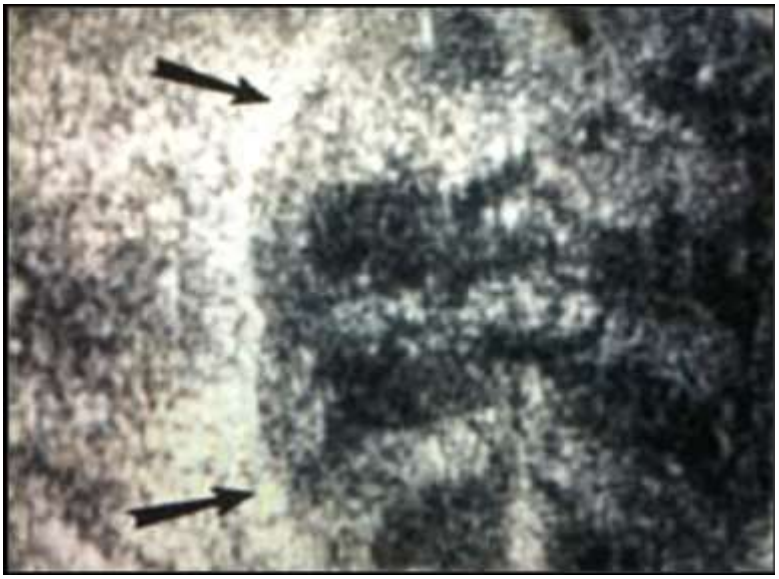

Fig 4: An ultrasound image of adrenal gland showing an enlarged, lobulated gland. It has a "cribriform" appearance on a newborn with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

Ultrasonography also helps identify mullerian structure. In a neonate, ambiguous genitalia, enlarged adrenal glands, and evidence of a uterus are virtually pathognomonic for CAH, also genitography helps determine ductal anatomy. Computed tomography (CT) and magnetic resonance imaging (MRI) are usually not indicated but may help identify internal organs. Histological analysis (laparoscopy or laparotomy) in certain case, may identify ovarian, testicular tissues, ovotestes or streak of gonads [52-46].

Management:

The issue should be discussed clearly and openly, and parents need to understand immediately that their child's genitalia are abnormal but can be corrected by surgery, and that the sex-of-rearing will be either a male or female, but this decision requires reasonable time for investigation. The announcement of the baby's sex should be deferred until supportive data are available. The embryology of sexual differentiation should be reviewed at a level that allows the parents to understand the issue at hand. Also, parents should understand that virilisation is reflective of the magnitude of androgen stimulation during foetal development, and is not necessarily indicative of the most appropriate sex-of-rearing. Establishing the genetic sex (karyotype) should be the first step, coupled with determining the anatomical status of the internal organs. Further specific hormonal investigations and therapeutic trials need to be undertaken to specify the cause of the anomaly and, hence, the appropriate therapy [3, 20, 36, 47, 52, 60-63].

The current Islamic recommendations put forward by the senior Ulama Council in Saudi Arabia as well as the experiences of local medical practitioners [64, 65] yield a set of very useful general guidelines. These recommendations are translated as follows:

1. A sex-change operation (i.e., converting someone with a completely developed gender to the opposite sex) is totally prohibited, and it is even considered criminal in accordance with the Holy Quran and the Prophet's sayings.
2. Those who have both male and female organs require further investigation, and if the evidence is more suggestive of a male gender, then it is permissible to treat the individual medically (by hormones or surgery) to eliminate his ambiguity and to raise him as a male. If the evidence is suggestive of a female gender, then it is permissible to treat her medically (by hormones or surgery) to eliminate her ambiguity and to raise her as a female.
3. Physicians must explain the results of medical investigations to the child's guardians and whether the evidence indicates that the child is male or female so that guardians are well-informed.
4. Therefore, genetically female children (46,XX karyotype) with normal ovaries and internal female organs (uterus, fallopian tubes, and upper vagina), but with some variable degree of virilisation of the external genitalia, should be raised as females; this decision is not only due to the ease of reconstruction of the female genitalia [66,67] but also due to the ability of these females to have high fertility rates and to bear children later in life [68] Any gender-reassignment surgery should generally be performed before 2 years of age, i.e., before the child develops gender-awareness. The techniques used for clitoral recession and vaginoplasty are continually improving. In contrast, a child with a sexual ambiguity and an XY chromosome creates a rather more difficult and challenging problem, not only for the child and his family but also for the medical caretaker. Although familial interactions with the young child during the first months of life are key factors in gender and sexual role-development, it is still difficult to predict the potential for penile growth in relation to future sexual function to determine if the male gender assignment will be satisfactory.

Also, it is important to understand that it is more difficult to reconstruct a penis than it is to create a vagina. The dominant role of the male gender in the Muslim community should not overrule Islamic Laws; these Laws should not be ignored, and they should be given prime consideration. There may exist a bias concerning the influence of the karyotype, such as the perception that a child with a 46,XY genotypes should be raised as a male. Patients with complete end-organ unresponsiveness due to androgen receptor defects (referred to as androgen insensitivity syndrome or testicular feminization) lack response to testosterone and, therefore, should be raised as females. It is advisable to remove the gonads at the time of diagnosis rather than wait until puberty, to avoid the adverse effects of testosterone on the neurons and to minimize the risk of the development of gonado blastoma [3] The availability of estrogen replacement therapy allows gender reassignment in such cases. However, the use of estrogen replacement therapy was debated recently, and it was suggested that the removal of gonads should be deferred until puberty to allow for estrogen formation, as carcinoma in situ is rare and the earliest reported case was at 14 years of age [4] On the other hand, in cases where genetic males demonstrate any appreciable response to exogenous stimulation, a testosterone treatment of short duration might indicate the degree of masculinisation achievable at puberty and facilitate the decision to raise such an individual as a male. In cases of 5-α-reductase deficiency, further virilisation occurs at puberty, along with the development of a male habitus. Many of these individuals will be fertile as adults; therefore, male gender is the appropriate choice for gender assignment, and surgical reconstruction should be performed at 18 months. [2, 3, 21] In testicular regression syndrome, gonadotrophic hormone deficiency, and other defective testosterone-synthesis pathways, a male gender should be assigned, and the appropriate medical therapy should be given.

In individuals with ovotesticular DSD (46,XX, 46,XY, or 46,XX/46,XY karyotypes), pure gonadal dysgenesis (46,XX or 46,XY karyotypes), or mixed gonadal dysgenesis (45,X/45,XY), there can be different degrees of internal and external genital formation, depending on the amount of functioning testicular tissue. The sex-of-rearing should be female in most of these cases, and all testicular tissue must be removed at the time of diagnosis because of the risk of virilisation at puberty and the higher incidence of gonadal tumours [3].

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