

Disorders of Sex Development: Diagnostic Approaches and Management Options—An Islamic Perspective

Nasir AM AL JURAYYAN

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Department of Paediatrics, College of Medicine & King Khalid University Hospital, King Saud University, PO Box 2925, Riyadh 11461, Saudi Arabia

Abstract

Ambiguous genitalia, currently defined as disorders of sex development (DSD), are not uncommon in the Muslim community. DSD constitute a complex, major social and medical emergency, as several forms of congenital adrenal hyperplasia can lead to significant salt loss, which may lead to shock if unrecognised and not appropriately treated. To ensure that the affected individual has a high quality of life (a successful outcome), medical practitioners must quickly and correctly assign the individual's gender and effectively assuage the family's concerns and anxieties. It is important to review and understand the embryology and physiology of sexual differentiation, and to understand the various aetiological causes of sexual ambiguity. In this review, the diagnostic approach and management of ambiguous genitalia is thoroughly discussed from an Islamic point of view.

Keywords: birth defects, case management, diagnosis, genitalia, Islam, sex development disorders

Introduction

Ambiguous genitalia, currently defined as disorders of sex development (DSD), constitute a complex, major social and medical emergency. Several forms of congenital adrenal hyperplasia can lead to significant salt loss, which, if unrecognised and not appropriately treated, may lead to shock. To ensure that the affected individual has a high quality of life (a successful outcome), medical practitioners must quickly and correctly assign the individual's gender and effectively assuage the family's concerns and anxieties (1–4). When approaching the treatment of any child diagnosed with sexual ambiguity, it is important to first review and understand the embryology and physiology of sexual differentiation. Although the basic developmental events have long been known, the genetic, biochemical, endocrine, and molecular mechanisms are complex and have only been partially elucidated (5–9).

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 (10–12). The gene for the anti-müllerian hormone (AMH) has been elucidated,

and a reliable assay for its measurement has been developed (13–15). 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 dihydrotestosterone (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 1. Genetically, sex is determined at fertilisation, 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 7th week, 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 2 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 feminisation (4–19).

Locally secreted testosterone promotes the development of the ipsilateral wolffian duct into the epididymis, vas deferens, ejaculatory duct, and seminal vesicle. Testosterone production by 1 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 contralateral testis (4,20,21). Thus, differences in the secretion of testosterone or AMH by the 2 gonads can result in the presence of male internal ducts on 1 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 (4,21). 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 1; however, labioscrotal fusion cannot be achieved after 12th week (21,22).

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 characterised by the presence of Fallopiian 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

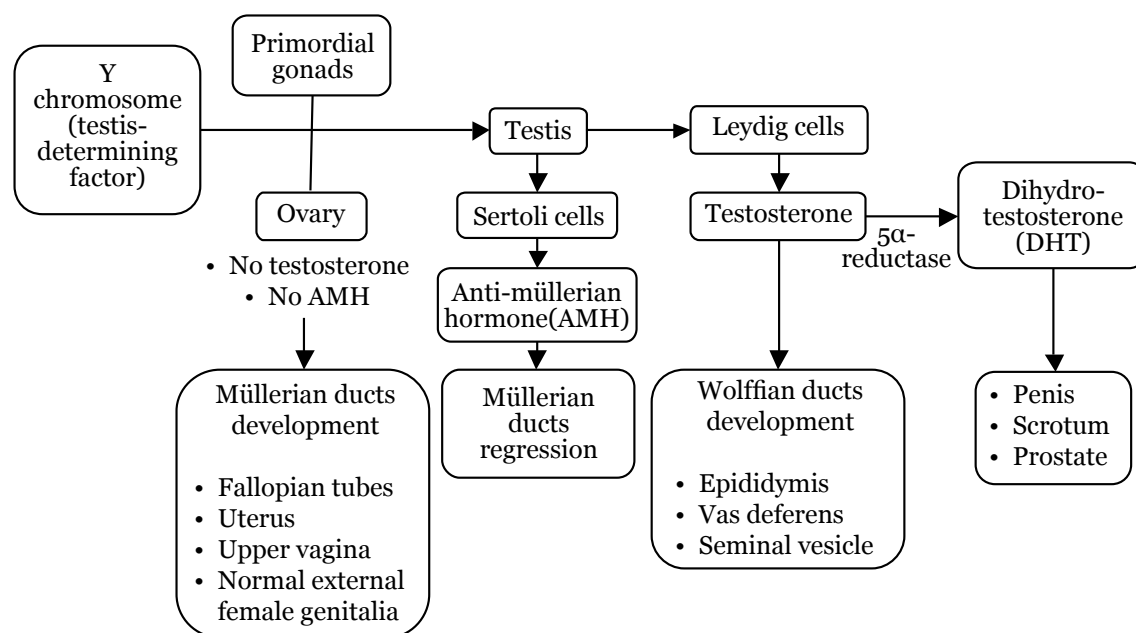


Figure 1: Simplified model for sexual differentiation and the development of internal and external genitalia.

Table 1: 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, perineoscrotal hypospadias, complete fusion of the labia majora
Type 5 (P-5)	Complete masculinisation (normal-looking male genitalia) but no palpable testes

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 (16,17,23–30). 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 (31). 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 (32).

Diagnostic approach and management

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 2 (1–4,33,37). Most patients are known to have either 46,XX DSD or 46,XY DSD conditions. In 46,XX DSD individuals (previously known as female-pseudohermaphrodites), 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 21 α -hydroxylase enzyme or due to deficiencies in the 11 β -hydroxylase and 3 β -hydroxysteroid dehydrogenase enzymes, constitutes the majority of DSD cases

(Figure 2). 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 (38–41). Saedi-Wong et al. (41) reported a high prevalence of congenital adrenal hyperplasia (54.3%) among the Saudi Arabian population. However, 46,XY DSD individuals (previously known as male pseudohermaphrodites) develop normal testes but with incomplete virilisation (under-masculinised external male genitalia, as shown in Figures 3, 4, and 5) 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 dysgenesis 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 (4,42). Ambiguous genitalia in genetic males may be comprised of multiple malformation syndromes, such as Smith–Lemli–Opitz, Vater, and Meckel's syndromes (43,44).

Table 2: Major causes of disorders of sex development (DSD) according to karyotype

46,XX Karyotype		
46,XX DSD	<ul style="list-style-type: none"> • Congenital adrenal hyperplasia (CAH) 	<ul style="list-style-type: none"> ◦ Enzyme deficiency <ul style="list-style-type: none"> ▪ 21α-hydroxylase ▪ 11β-hydroxylase ▪ 3β-hydroxysteroid dehydrogenase
	<ul style="list-style-type: none"> • Ovarian/adrenal tumours (mother–child) 	
	<ul style="list-style-type: none"> • Exposure to exogenous medication (synthetic progestin preparation) 	
Ovotesticular DSD		
46,XY Karyotype		
46,XY DSD	<ul style="list-style-type: none"> • Lack of synthesis of testosterone 	<ul style="list-style-type: none"> ◦ Testicular differentiation <ul style="list-style-type: none"> ▪ pure gonadal dysgenesis ▪ absence of Leydig cells or luteinising hormone receptor ▪ testicular regression ▪ gonadotrophin hormone deficiency ◦ Enzyme deficiency in testosterone pathway <ul style="list-style-type: none"> ▪ 20,22-desmolase ▪ 17,20-lyase ▪ 3β-hydroxysteroid dehydrogenase ▪ 17α-ketoreductase
	<ul style="list-style-type: none"> • Lack of synthesis of dihydrotestosterone 	<ul style="list-style-type: none"> ◦ 5α-reductase deficiency
	<ul style="list-style-type: none"> • End-organ-unresponsiveness (resistance) 	<ul style="list-style-type: none"> ◦ Partial ◦ Complete
Ovotesticular DSD		
Multiple or local congenital anomalies		
Mixed Karyotype		
Ovotesticular DSD 46,XX/46,XY		
Mixed gonadal dysgenesis 45,X/46,XY		

Thus, the presence of other morphogenic anomalies usually indicates a non-endocrine explanation for the abnormal appearance of the genitalia (4). Furthermore, local ano-rectal and uro-genital anomalies such as epispadias and bladder extrophy are known to be associated with external genital ambiguity (4,43–45).

The initial assessment of a DSD patient requires a detailed maternal and family history, as well as a careful physical examination for

symptoms including hyperpigmentation and signs of salt-wasting; the initial assessment should also provide documentation of the existing external genitalia (1,3,4,33–37). 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 specialised physicians are available. A multidisciplinary



Figure 2: Ambiguous genitalia in a 46,XX patient known to have congenital adrenal hyperplasia due to 21α -hydroxylase deficiency. Note the complete masculinisation, with normal looking hyperpigmented male genitalia (but no palpable testes).



Figure 3: Ambiguous genitalia in a 46,XY patient known to have congenital adrenal hyperplasia due to 3β -hydroxysteroid dehydrogenase deficiency. Note the pigmented, short, curved phallus, central urogenital slit, and separated labioscrotal testis.

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.

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 (3,4,33,46). A paediatric radiologist plays a significant role in elucidating the existing anatomy. Real-time pelvic ultrasonography (US) is not invasive, and this technique remains the modality of choice for such screening; however, US (Figures 6) performed in conjunction with genitography (Figure 7), which reveals further details of the vaginal structures, is far more informative than US alone (47). Magnetic resonance imaging (MRI) is helpful in cases where US and US/genitography examinations are inconclusive (48). Pelvic laparotomy or laparoscopy and gonadal biopsy are rarely needed.

The current Islamic recommendations put forward by the senior Ulama Council in Saudi Arabia as well as the experiences of local medical practitioners (3,4,46,49) yield a set of very useful general guidelines. These recommendations are translated as follows:



Figure 4: Ambiguous genitalia in a 46,XY patient known to have partial androgen insensitivity. Note the micropenis, urogenital sinus, and labioscrotal folds (the left fold contains a palpable gonad).



Figure 5: Ambiguous genitalia in a 46,XY patient known to have gonadotrophin hormone deficiency. Note the micropenis, underdeveloped scrotum, and bilateral undescended testes



Figure 6: Ultrasound of the sagittal pelvis showing the bladder (BL) from an anterior view, uterus (UT) from a postero-superior view, and vagina (V) from a postero-inferior view.

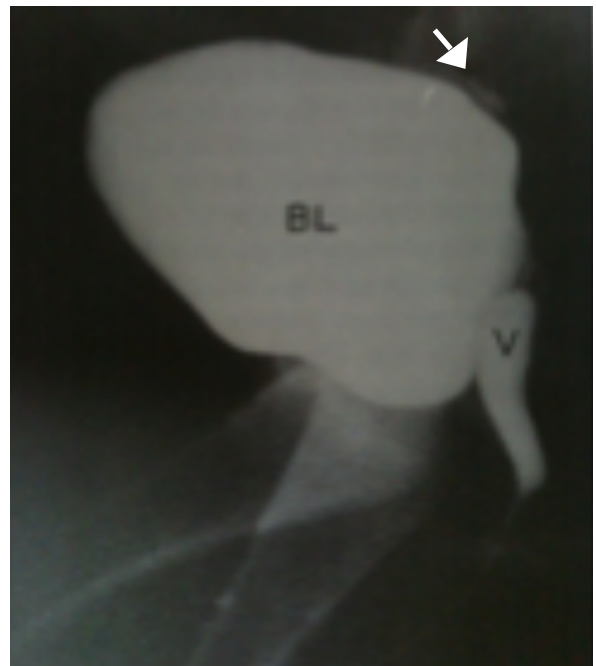


Figure 7: A genitogram showing contrast material filling the bladder (BL), vagina (V), and uterus (arrow).

- 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.

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 (50–52), but also due to the ability of these females to have high fertility rates and to bear children later in life (53). 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 feminisation) 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 minimise the risk of the development of gonadoblastoma (4). The availability of oestrogen replacement therapy allows gender reassignment in such cases. However, the use of oestrogen replacement therapy was debated recently, and it was suggested that the removal of gonads should be deferred until puberty to allow for oestrogen formation, as carcinoma in situ is rare and the earliest reported case was at 14 years of age (37). 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 (2,4,21). 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 (4).

In conclusion, appropriate genetic and psychosocial counselling should be made available to the family and when the patient is old enough to understand, all available information should be progressively disclosed.

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Correspondence

Professor Dr Nasir AM Al Jurayyan
MBBS (King Saud University), FRCPC, FAAP
Department of Pediatrics
College of Medicine & King Khalid University Hospital
King Saud University
PO Box 2925
Riyadh 11461
Saudi Arabia
Tel: +966-1-467-1504
Fax: +966-1-467-1631
Email: njurayyan@ksu.edu.sa

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