Imaging Evaluation of Disorders of Sex Development

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Abstract

Disorders of sex development (DSD) refer to congenital conditions with atypical development of chromosomal, gonadal, or anatomic sex. In the revised classification of DSD, there are three categories based on karyotype: 46,XX DSD; 46,XY DSD; and sex chromosome DSD. Imaging, as part of a multidisciplinary approach to management of DSD, has a key role in gender assignment. The main role of imaging is to help in identifying the gonads and the Müllerian structures. Ultrasound is useful, especially in the neonate with ambiguous genitalia. Magnetic resonance imaging is a useful modality to locate and characterize the gonads in young girls with primary amenorrhea and also to identify streak gonads, which have a risk of malignancy.

Keywords
► disorders of sex development
► DSD
► imaging
► ambiguous genitalia
► gonads

Introduction

Disorders of sex development (DSD), as defined by the Chicago Consensus of 2006, are congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical.[1] The term DSD replaces the older nomenclature of "Intersex disorders."[1] While majority of individuals with DSD present at birth with ambiguous genitalia, some may present at adolescence or later life, with delayed puberty, primary amenorrhea, or virilization.[2] The incidence of ambiguous genitalia is 1 per 4500 births.[3] The diagnosis of DSD in a newborn can be distressing to the parents and family. A multidisciplinary approach is needed to evaluate these patients with the use of ethical principles to minimize physical and psychological risks ,to preserve potential fertility and ability to have satisfactory sexual relationships and with a respect for parental desires and beliefs.[4] One of the most important aspect of management is gender assignment, which is done after a complete evaluation. Imaging plays an important role in gender assignment by delineating the anatomy of genital tract and identifying the gonads. This review aims to highlight the revised classification of DSD with examples.

Imaging Modalities

Ultrasound

Ultrasound is the primary imaging modality, especially in the neonate with ambiguous genitalia. It is useful in identifying the gonads, the presence or absence of uterus and presence of a hydrocolpos (►**Fig. 1**). The kidneys and adrenal glands in the neonate are also evaluated using ultrasound.[5]

Genitogram

Genitogram is useful to delineate the presence of urogenital sinus (►**Fig. 2**), which may be associated with DSD. It is also useful to locate the vagina, delineate the level at which vagina opens into sinus and to identify a male or female configuration of urethra.[4,5] The normal male urethra has a longer horizontal anterior urethra, the ratio of the horizontal anterior urethra to vertical posterior urethra being 3:2 and hence, this ratio can be used to assess the degree of virilization in a female. Verumontanum is also seen in prostatic part of male urethra.[4]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a useful modality, because of its superior soft tissue resolution and multiplanar imaging capabilities. It is useful in locating the gonads and presence of ectopic or streak gonads. MRI is more sensitive than ultrasound in localization of the gonads, although it has comparable sensitivity to ultrasound for internal genitalia.[6] Streak gonads may appear as low signal intensity stripes on T2-weighted images (►**Fig. 3**).[4,5]

Computed Tomography

Computed tomography is useful in the evaluation of neoplasms associated with streak gonads.[4]

Development

The pathway of normal genital development is shown in ►**Fig. 4**.

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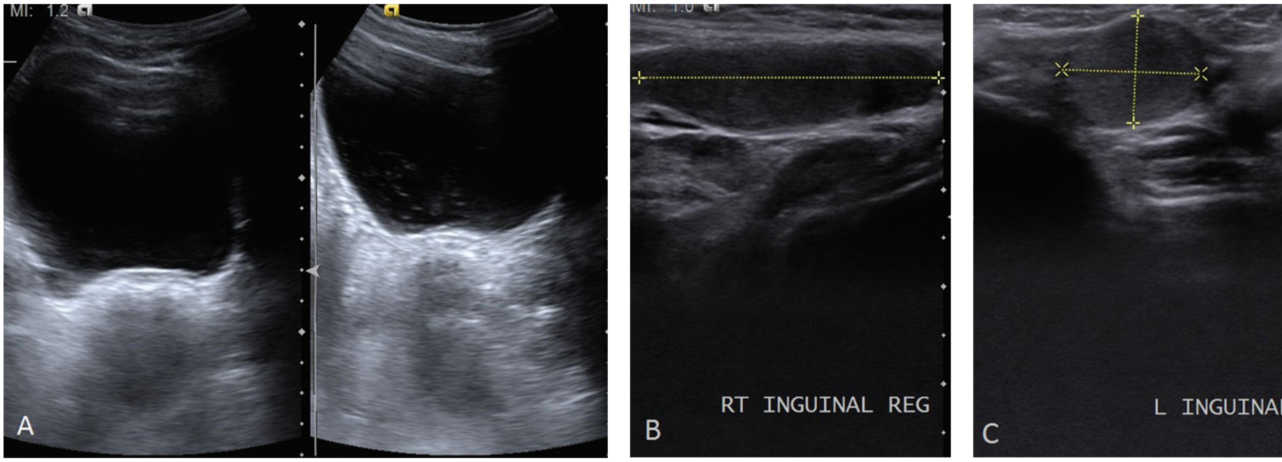

Fig. 1 Ultrasound images of a 14-year-old girl with primary amenorrhea shows (**A**) absent uterus and (**B**, **C**) both the testes seen in inguinal regions.

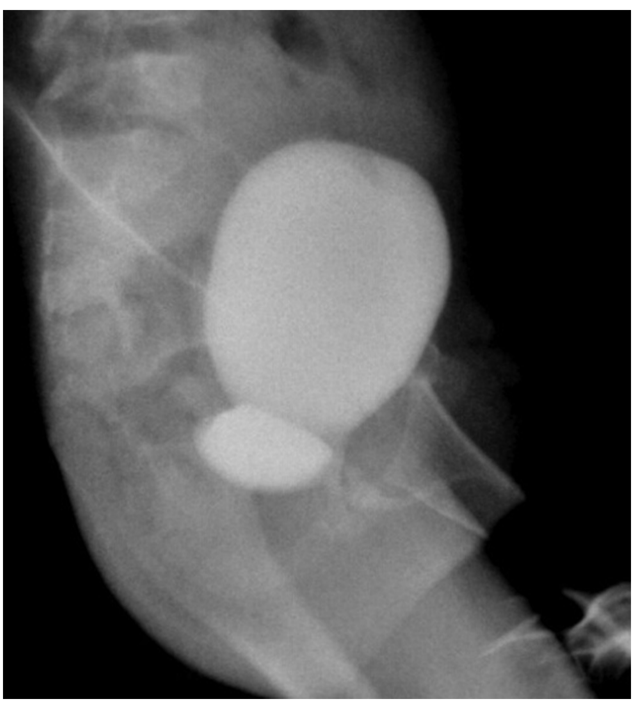

Fig. 2 Genitogram of a 7-year-old girl with only two perineal openings. Contrast injected through the anterior opening confirms presence of a persistent urogenital sinus with opacification of bladder and distended vagina posterior to the bladder.

Fig. 3 High-resolution T2-weighted sagittal magnetic resonance imaging of a 4-year-old child with female phenotype raised as a girl shows absence of uterus.

►**Table 1** shows the revised nomenclature of DSD. DSD are divided into three main categories, based on the karyotype; 46,XX DSD; 46,XY DSD; and sex chromosome DSD.[1,2] Each of these categories is further classified, based on underlying etiology. ►**Figure 5** shows the revised classification of DSD.

46XX Disorders of Sex Development

►**Table 2** shows the classification of 46XX DSD, the most common disorder being congenital adrenal hyperplasia (CAH).

Congenital Adrenal Hyperplasia

The commonest cause for 46,XX DSD is CAH, resulting in virilization of the female fetus.[4] The presence of ambiguous genitalia in an infant with nonpalpable gonads should raise the suspicion of CAH.

CAH is an autosomal recessive disorder where there is disordered steroidogenesis due to deficiency of enzymes involved in the adrenal steroid biosynthesis pathway.

Deficiency of 21-hydroxylase, which is the most common enzyme involved and also 11-β hydroxylase, results in deficient adrenal steroid biosynthesis, namely cortisol and aldosterone.

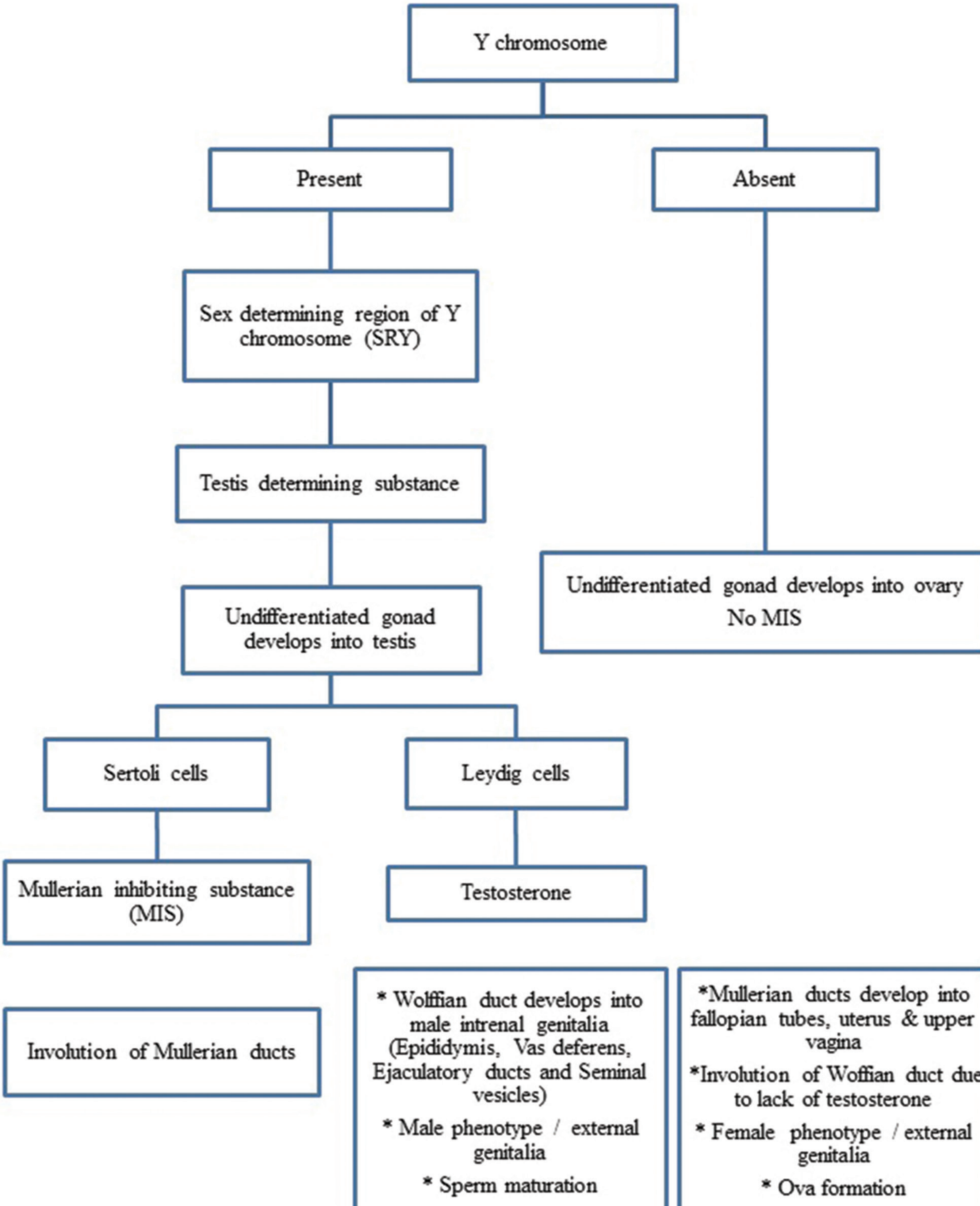

Fig. 4 Flowchart with pathway of normal genital development.[5]

This leads to excess adrenocorticotropic hormone release causing adrenal hyperplasia and accumulation of steroid precursors that are shunted to produce androgens by adrenals, resulting in androgen excess.

In the female fetus, exposure to excess androgens produced by adrenals causes ambiguous genitalia and urogenital sinus malformations. Salt wasting from mineralocorticoid deficiency can also occur in the neonatal period.[7,8]

Table 1 Revised nomenclature related to DSD[1]

Revised nomenclature related to DSD	Previous
46,XY DSD	Male pseudohermaphrodite
46,XX DSD	Female pseudohermaphrodite
Ovotesticular DSD	True hermaphrodite
46,XX testicular DSD	XX male
46,XY complete gonadal dysgenesis	XY sex reversal

Abbreviation: DSD, disorders of sex development.

Ultrasound is the imaging modality of choice in the evaluation of CAH.

Adrenals

Ultrasound is useful to evaluate the enlarged adrenals. CAH is characterized by enlarged adrenals with adrenal length and width exceeding 20 and 4 mm, respectively, and normal corticomedullary differentiation with central medulla that is echogenic and a rim of hypoechoic cortex. However, the presence of normal sized adrenals on ultrasound does not exclude CAH.[9,10] A cerebriform appearance (►**Fig. 6**) of adrenal glands is specific for CAH.[11]

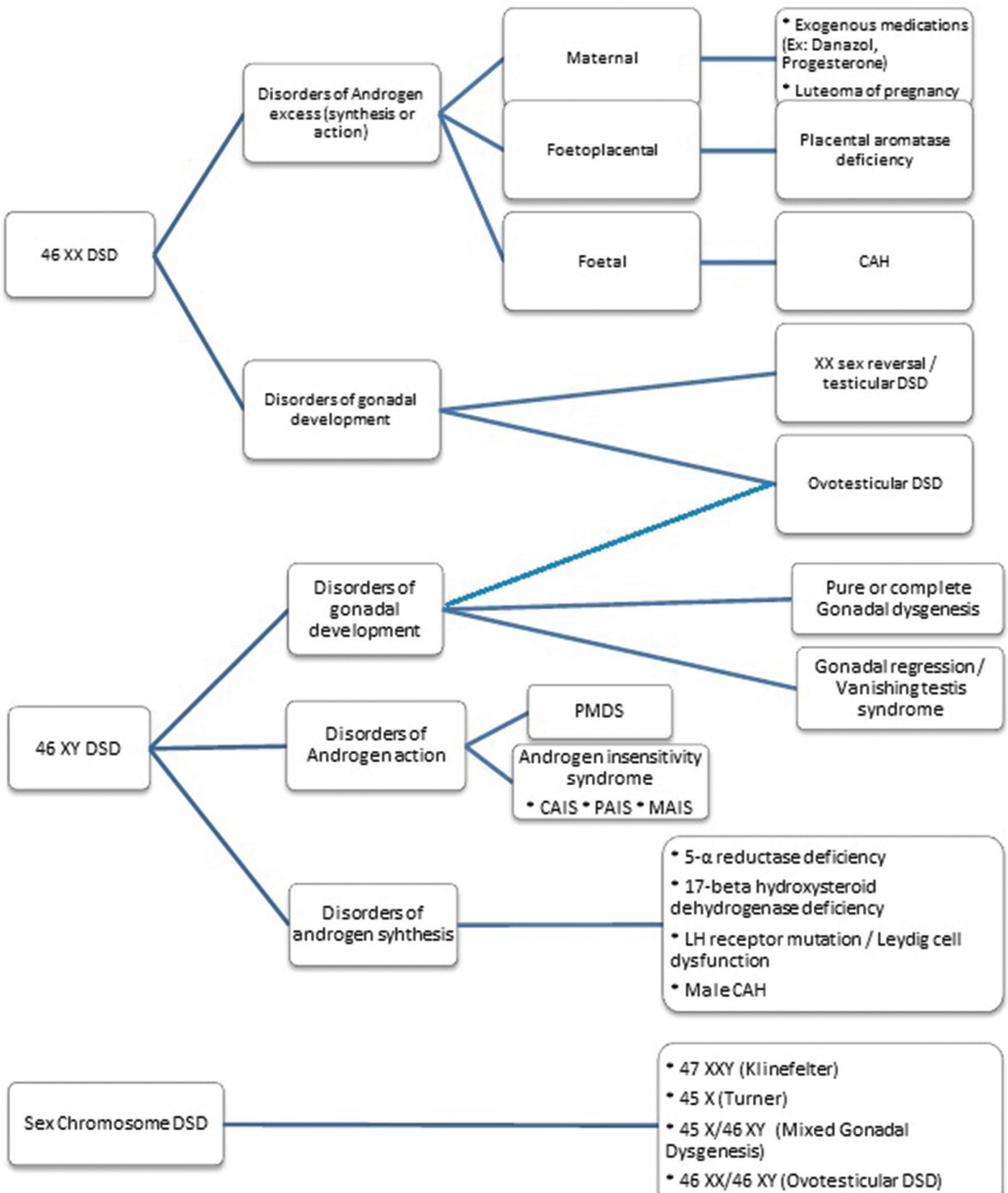

Fig. 5 Flowchart with revised classification of DSD. CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; MAIS, mild androgen insensitivity syndrome; PAIS, partial androgen insensitivity syndrome; PMDS, Persistent Mullerian Duct syndrome.

Uterus

In an infant with ambiguous genitalia, identification of the uterus and ovaries on ultrasound will confirm the presence of 46,XX DSD, resulting from androgen excess. Ultrasound is also useful to identify hydrocolpos (►**Fig. 7**) due to urogenital sinus malformation.[10]

Urogenital Sinus

Urogenital sinus forms the ventral part of cloaca after it separates from anal canal during fourth to seventh week of development. This gives rise to the bladder, urethra, and prostate in the male and bladder, and urethra and distal one-third of the vagina in the female. Urogenital sinus malformations occur when there is excess exposure of fetus to androgens. This malformation results in a common channel into which the vagina and urethra open and only two perineal openings in a female infant.[5]

Genitogram (►**Fig. 8**) is useful in evaluation of urogenital sinus malformation by delineating the common channel. It provides information on its length,location of the vaginal confluence,distance from bladder neck,all of which may influence management.[4]

Table 2 Classification of 46XX DSD[2]

46XX DSD	
Disorders of gonadal development	Ovotesticular DSD XX sex reversal (testicular DSD) Gonadal dysgenesis
Disorders related to androgen synthesis or action	*Androgen excess* Maternal—luteoma, exogenous (medications) Fetoplacental—aromatase deficiency Fetal—Congenital adrenal hyperplasia (enzyme deficiency:21-hydroxylase most common, 11 β-hydroxylase)

Abbreviation: DSD, disorders of sex development.

Ovotesticular DSD

Ovotesticular DSD, earlier referred to as true hermaphroditism, is a rare form of DSD, with an incidence of 1 per 100,000 live births.[12] Genetically, majority of these individuals are 46XX with other less common karyotypes including 46,XX/XY mosaicism and rarely 46XY.[12,13] This disorder is characterized by presence of ovarian tissue with primordial follicles and testicular tissues with seminiferous tubules, within the same individual. Clinical features, which depend on karyotype, can vary from genital ambiguity, cryptorchidism, gynecomastia, and cyclical hematuria. The commonest presentation is the presence of both these tissue types within the same gonad or an ovotestis.[14]

Imaging

On ultrasound, an ovotestis will show a mixed or heterogenous pattern with a portion representing testis appearing solid and a portion resembling ovary with follicles.[15]

Other combinations of ovary on one side and testis on the other or ovary/testis with ovotestis may be seen (►**Fig. 9**). The uterus is present in most of these individuals. The type of internal genitalia will be influenced by the adjacent gonad. A testis will be accompanied by adjacent vas deferens and epididymis and fallopian tube will be seen on side of ovary.[14]

46XY Disorders of Sex Development

►**Table 3** shows the classification of 46XY DSD. The most common disorders of the 46XY DSD are as follows.

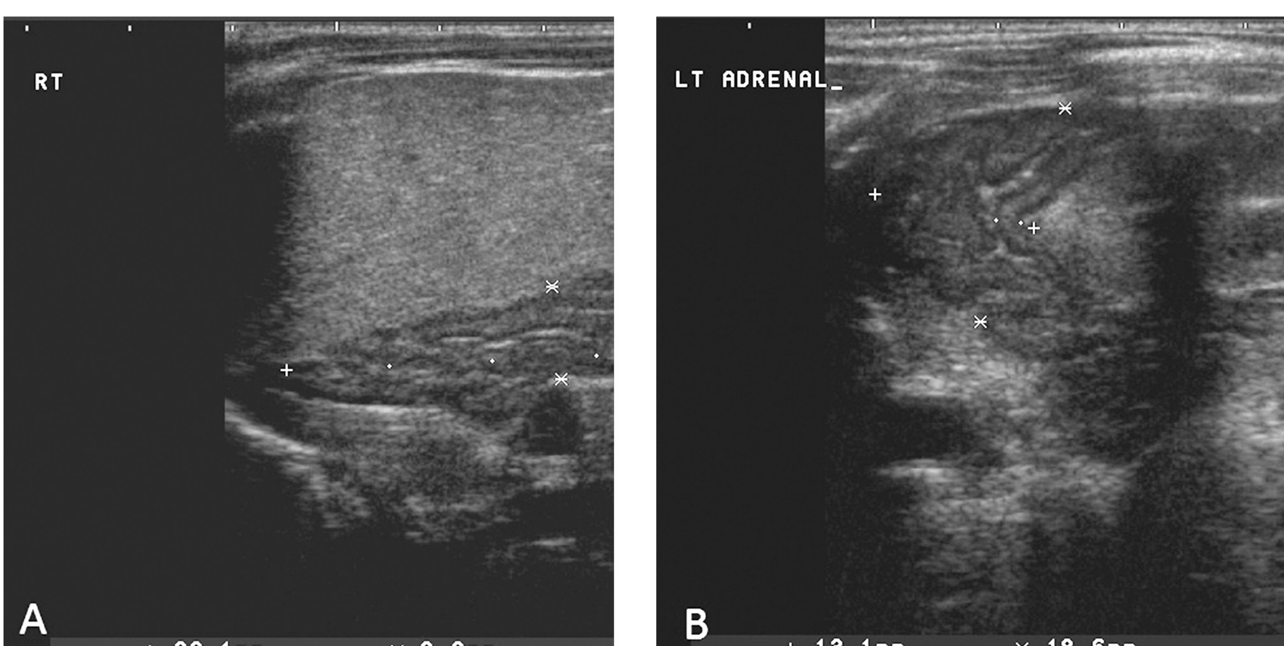

Fig. 6 High-resolution ultrasound of a neonate with congenital adrenal hyperplasia showing typical cerebriform appearance of the adrenal glands. (**A**) Right adrenal gland and (**B**) left adrenal gland.

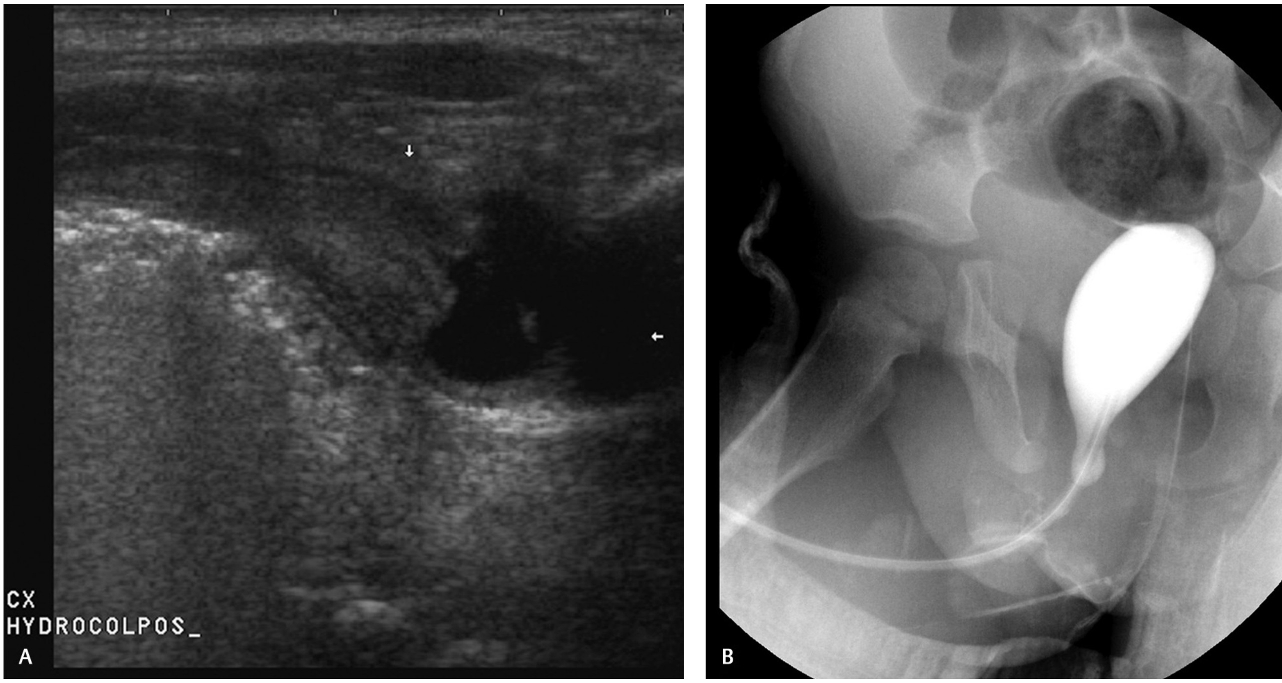

Fig. 7 Ultrasound (**A**) and genitogram (**B**) of an infant with congenital adrenal hyperplasia, ambiguous genitalia, and urogenital sinus malformation confirms presence of uterus and hydrocolpos.

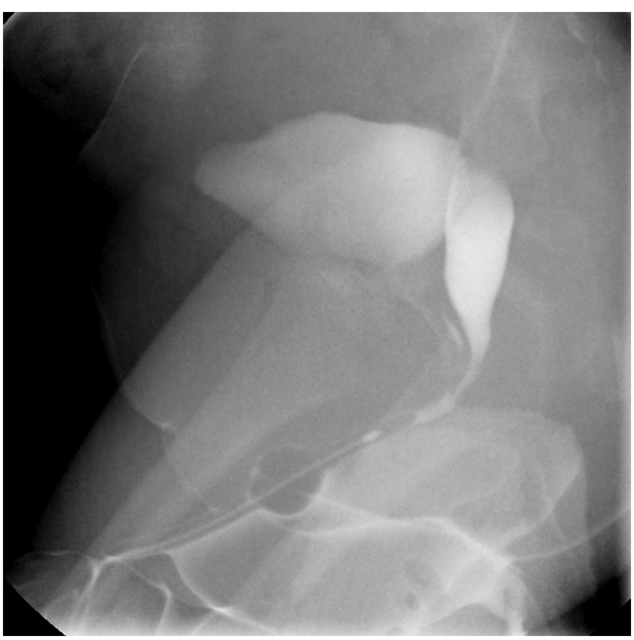

Fig. 8 Genitogram of an infant with persistent urogenital sinus shows opacification of bladder and vagina posterior to bladder, after injection of contrast through a common perineal opening.

Disorders of Androgen action

Androgen Insensitivity Syndrome

This condition was first described by John Morris in 1953 who called it the testicular feminization syndrome. This has been replaced by the current accepted terminology of androgen insensitivity syndrome.[16] It is an X linked recessive disorder in which mutations of the androgen receptor occur, as a result of which there is resistance to action of androgen. This 46,XY DSD is characterized by normal testicular development,normal androgen biosynthesis by the testes, but the receptor mediated action of the androgen is defective.[17] Depending on the type of androgen receptor mutations, it is further subclassified into complete androgen insensitivity syndrome (CAIS), partial (PAIS), or mild (MAIS).[18]

Complete Androgen Insensitivity Syndrome

This disorder has a prevalence of 1 to 5/100,000 genetic males.[18] These individuals present with primary amenorrhea with a female phenotype at birth with female external genitalia while gender identity karyotype in these individuals is 46,XY.

Imaging

The testis, which are normally developed in these individuals, can be seen on imaging. Both ultrasound and MRI are useful to locate the testes, which may be inguinal, intra-abdominal, or labial in location. An inguinal hernia in a young girl with testis as content may be another presentation.[18]

MRI is superior to ultrasound to locate the intra-abdominal testis, seen in majority of patients with CAIS. Since testes are normal in development, there is production of Müllerian-inhibiting factor by Sertoli cells with failure of development of Müllerian structures.[18,19] Hence imaging will show absence of uterus, fallopian tube, and upper vagina. A short blind ending vagina may be present.[19]

MRI is useful to locate the gonads.This helps to plan gonadectomy and also in surveillance,as this disorder can predispose to malignancy. Normal testes have homogenous high signal intensity on T2-weighted MRI and intermediate signal intensity on T1-weighted images. Testicular malignancy will be seen as low T2-weighted signal intensity with disappearance of testicular septa.[18,20] The testes in CAIS have intermediate signal intensity on T2-weighted

MRI, resembling normal undescended testis (►**Fig. 10**). Other imaging features include paratesticular cysts and Sertoli cell adenomas that are low signal intensity areas on MRI.[18,20]

Partial Androgen Insensitivity

This disorder is characterized by genital ambiguity or varying amounts of virilization. Imaging will confirm the presence of descended or undescended testis. Müllerian structures are absent. (►**Fig. 11**).[19]

Mild Androgen Insensitivity Syndrome

This is also known as "undervirilized male syndrome" and is characterized by decreased virilization at puberty and infertility. Imaging will show no genital abnormality. Müllerian structures will be absent.[19]

Persistent Müllerian Duct Syndrome

This is a form of 46,XY DSD resulting from deficiency of the anti-Müllerian hormone that is responsible for involution of the Müllerian duct during embryonic life. Hence, in a genetically male individual with male phenotype or external genitalia, there is persistence of the Müllerian derivatives, namely, the uterus, fallopian tube, and upper vagina. The commonest presentation is unilateral undescended testis and contralateral hernia uteri inguinalis.[21] ►**Figure 12** is an example of persistent Müllerian duct syndrome.

Table 3 Classification of 46XY DSD[2]

46XY DSD	
Disorders of gonadal development	Pure/complete gonadal dysgenesis Partial gonadal dysgenesis Ovotesticular DSD Gonadal regression or vanishing testes syndrome
Disorders related to androgen synthesis or action	*Androgen action* Androgen insensitivity syndrome *Androgen synthesis* LH receptor mutation 17-β hydroxysteroid dehydrogenase deficiency 5-α reductase deficiency Male CAH

Abbreviations: CAH, congenital adrenal hyperplasia; DSD, disorders of sex development; LH, luteinizing hormone.

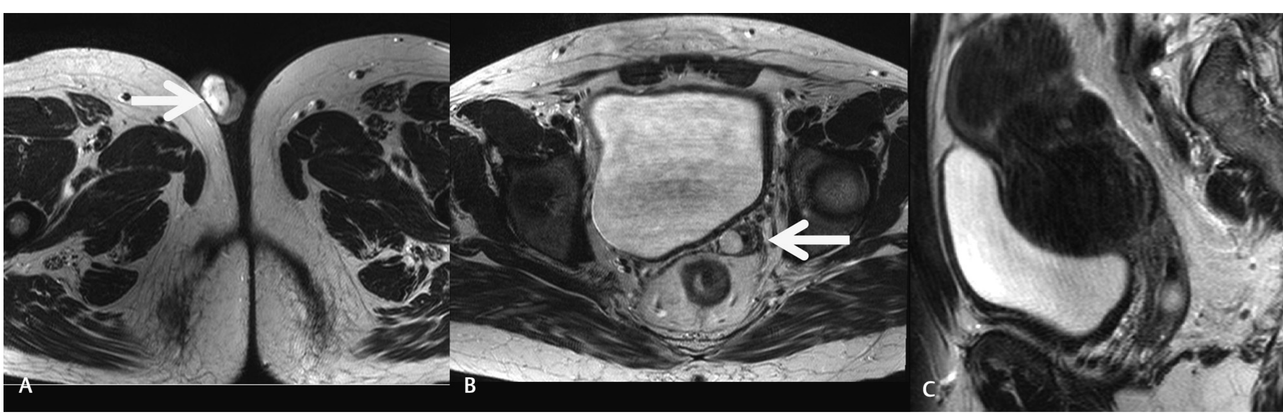

Fig. 9 Magnetic resonance imaging of a patient with ovotesticular disorders of sex development. (**A**) T2-weighted high-resolution axial image of the scrotum shows right testis in the right hemiscrotum. (**B**) T2 high-resolution image of pelvis shows ovary with follicles in left hemi pelvis, which was confirmed on histology. (**C**) T2 high-resolution sagittal image of pelvis shows presence of uterus.

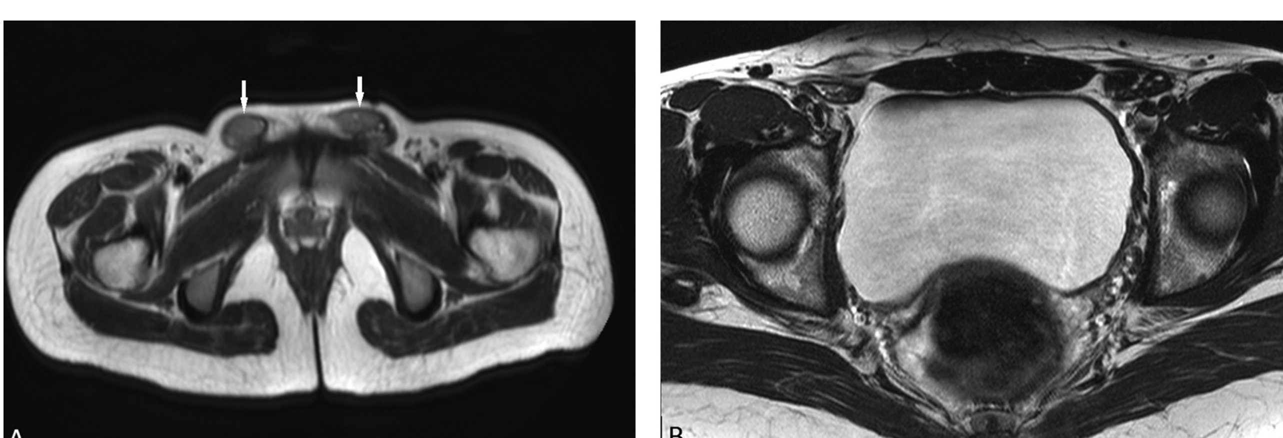

Fig. 10 A 17-year-old girl with complete androgen insensitivity syndrome presented with primary amenorrhea and female phenotype. (**A**) T2-weighted axial magnetic resonance imagings shows testes in the inguinal canals on both sides (arrows) and (**B**) absent uterus and ovaries.

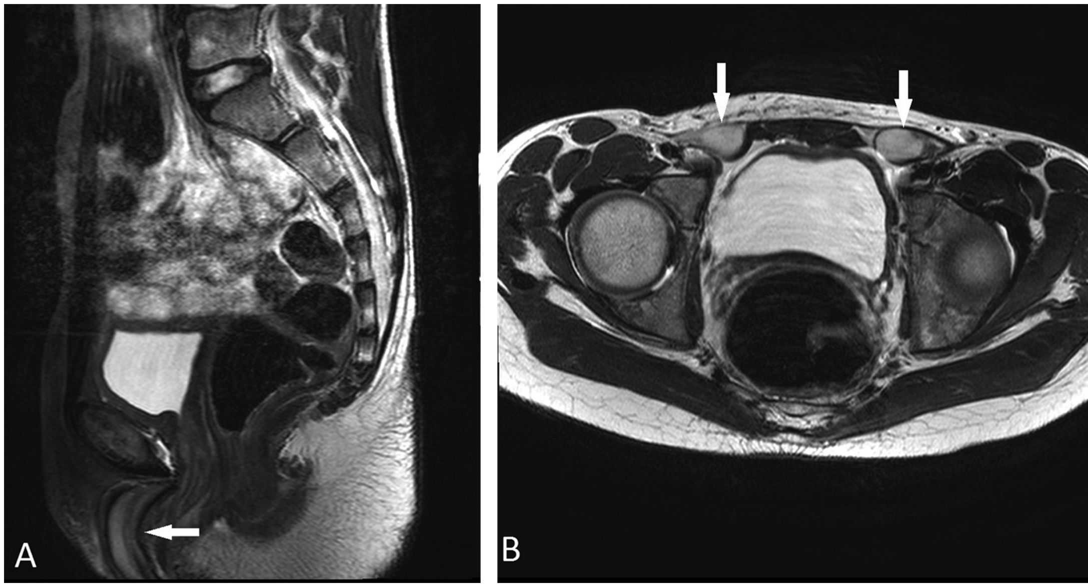

Fig. 11 A 15-year-old girl with partial androgen insensitivity syndrome presented with ambiguous genitalia and primary amenorrhea. Ultrasound revealed presence of both testes in the inguinal region (not shown). (**A**, **B**) T2-weighted sagittal and axial magnetic resonance imaging reveals enlarged phallus (arrow in A) with absent uterus and both testes visualized in the upper inguinal canal (arrows in **B**).

Disorders of Androgen Synthesis

These may result from enzyme deficiencies in the biosynthetic pathway of production of testosterone such as 5-α reductase deficiency, 17-β hydroxysteroid dehydrogenase deficiency, or Leydig cell dysfunction.[17]

5-α Reductase Deficiency

The enzyme 5-α reductase converts testosterone to dihydrotestosterone, the potent form of the androgen. Deficiency of the enzyme will result in elevated testosterone to dihydrotestosterone ratio. Clinically, there is genital ambiguity.

Imaging confirms presence of testes that are usually inguinal, labial or scrotal, and extra-abdominal. The Müllerian structures are absent although a short, blind ending vagina may be present.[17]

17-β Hydroxysteroid Dehydrogenase Deficiency

17-beta hydroxysteroid dehydrogenase deficiency is a rare disorder, affected individuals present with varying degrees of genital ambiguity or virilization at puberty.

Leydig Cell Dysfunction

Leydig cell dysfunction results from failure of the luteinizing hormone receptor, which is needed to stimulate Leydig cells. Imaging will show absence of Müllerian structures and presence of testes.[17]

Defect in Gonadal Development

Pure 46, XY Gonadal Dysgenesis

Pure 46, XY gonadal dysgenesis or Swyer syndrome was first described by Swyer in 1955 with an incidence of ~1 in 80,000 births.[22] About 10 to 15% of individuals show mutations in the SRY gene. This disorder is characterized by completely dysgenetic or streak gonads that do not produce hormones. In the absence of testosterone, there is no virilization and there is completely female phenotype or external genitalia. These individuals are, hence, raised as girls who will present with primary amenorrhea.[22,23]

Imaging

The absence of anti-Müllerian hormone results in development of uterus, fallopian tubes, and vagina. Imaging will reveal a small sized uterus (►**Fig. 13**). The streak gonads may be difficult to identify. MRI is the most useful imaging modality to identify the streak gonads that are seen as hypointense stripes on T2-weighted MRI.[5] There is an increased risk of germ cell tumors in Swyer syndrome; most common tumors are gonadoblastoma, dysgerminoma, and less commonly seminoma. Hence, there is a need to locate streak gonads and to remove them early.[23]

►**Figure 14** and ►**Table 4** show the features of 46,XY DSD with female phenotype and primary amenorrhea.

Sex Chromosome DSD

►**Table 5** shows the classification of sex chromosome DSD.

Mixed Gonadal Dysgenesis

45,X/46,XY Mixed gonadal dysgenesis is a disorder resulting from abnormality in number of sex chromosomes, most common karyotype being 45,X/46,XY mosaicism.[23]

The affected individuals present with ambiguous genitalia.

Imaging will reveal a testis on one side and a dysgenetic or streak gonad on the other side that histologically contains ovarian stroma without follicles. Fallopian tube is usually seen on the side of the streak gonad. On the side of the testis, fallopian tube is absent due to local action of anti-Müllerian hormone from testis.[26] The streak gonads, although difficult to identify, must be located and removed

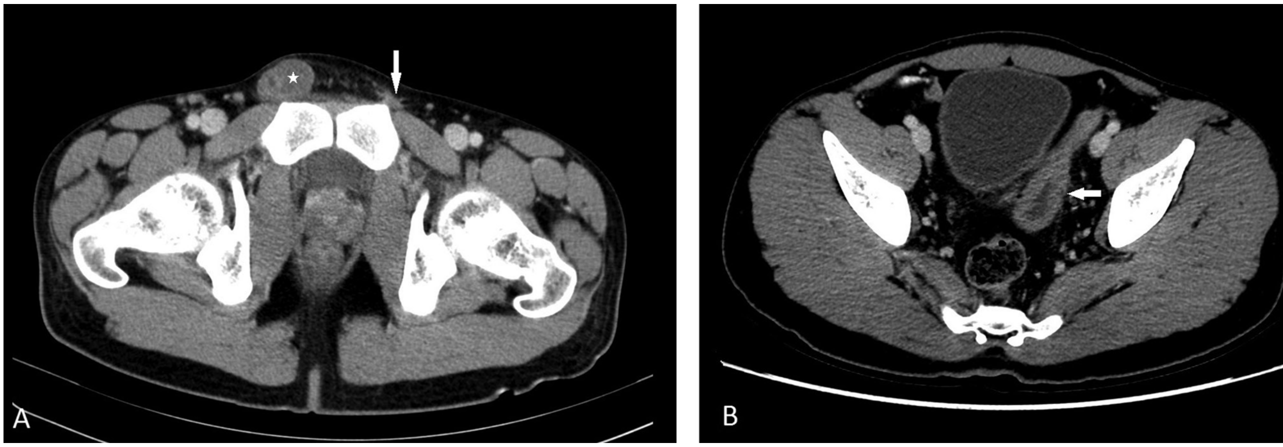

Fig. 12 A 22-year-old male with persistent Müllerian duct syndrome. Computed tomography shows (**A**) right undescended testis (*) and surgical scar (arrow) from previous orchidectomy for germ cell tumor in undescended testis and (**B**) a tubular structure suggestive of uterus (arrow) located posterior to the bladder.

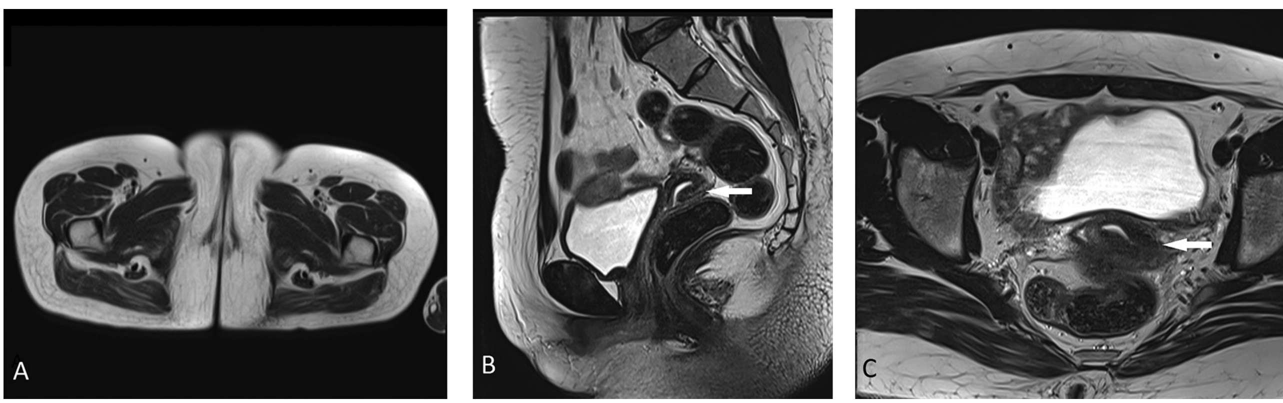

Fig. 13 A 30-year-old married patient with 46,XY pure gonadal dysgenesis, presenting with primary amenorrhea. (**A**) T2-weighted magnetic resonance imaging (MRI) through the pelvis shows a female phenotype. (**B**, **C**) T2-weighted sagittal and axial MRI shows presence of uterus (arrow) and nonvisualized gonads.

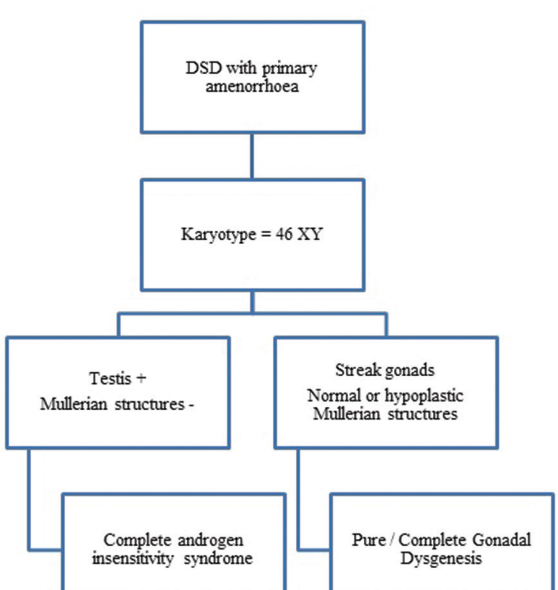

Fig. 14 Flowchart illustrates differences in 46,XY disorders of sex development (DSD) presenting with female phenotype and primary amenorrhea.

Table 4 46,XY DSD presenting with primary amenorrhea[18,24]

	Complete androgen insensitivity	Pure 46,XY gonadal dysgenesis
Karyotype	46,XY	46,XY
Cause	Androgen receptor mutation	Androgen deficiency
Defect	Androgen receptor insensitivity	Dysgenetic gonad
Laboratory marker	Normal testosterone	Decreased basal testosterone Decreased MIS Elevated basal FSH, LH Minimal or no elevation of testosterone on hCG stimulation test
Gonad	Testis	Streak gonads
Uterus	Absent	Present

Abbreviations: CAH, congenital adrenal hyperplasia; DSD, disorders of sex development; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MIS, Müllerian inhibiting substance.

due to the risk of gonadal neoplasms. Rudimentary uterus is usually present.

DSD presenting with ambiguous genitalia at birth are summarized in ►**Fig. 15** and ►**Table 6**.

Table 5 Classification of sex chromosome DSD[25]

47, XXY	Klinefelter syndrome and variants
45,X	Turner syndrome and variants
45, X/46,XY	Mixed gonadal dysgenesis, ovotesticular DSD
46, XX/46,XY	Chimeric ovotesticular DSD

Abbreviation: DSD, disorders of sex development.

Gonadal Neoplasms

The presence of dysgenetic or streak gonads with Y chromosome is a risk factor for the development of gonadoblastoma. This is a benign germ cell tumor that can later transform to malignancy, commonly dysgerminoma (►**Fig. 16**). Other germ cell tumors that can occur from gonadoblastoma are yolk sac tumor, seminoma, immature teratoma, embryonal carcinoma,

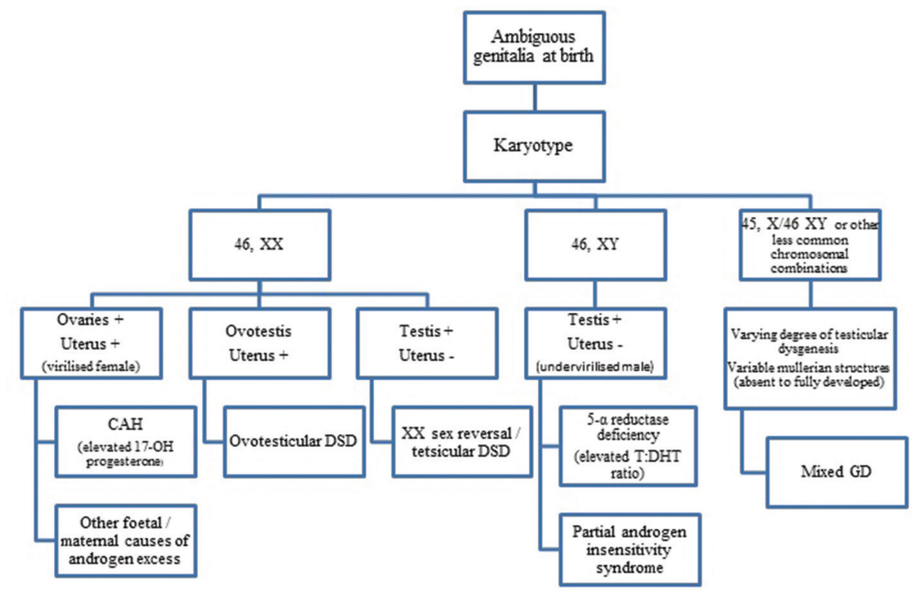

Fig. 15 Flowchart of DSD with ambiguous genitalia at birth. CAH, congenital adrenal hyperplasia; DHT, dihydrotestosterone; DSD, disorders of sex development; GD, gonadal dysgenesis.

Table 6 Simplified approach to a neonate with ambiguous genitalia[3,17,24]

	CAH	Ovotesticular DSD	Partial androgen insensitivity	5-α reductase deficiency	Mixed gonadal dysgenesis
Karyotype	46,XX	46,XX (most common) 46,XX/46,XY 46,XY (rare)	46,XY	46,XY	45,X/46,XY
Cause	Androgen excess	Androgen excess	Androgen receptor mutation	Androgen deficiency	Androgen deficiency
Source	Fetal adrenal	Testis/ovotestis	–	–	–
Defect	21-hydroxylase deficiency (most common)	Defect in gonadal synthesis	Androgen receptor insensitivity	5-α reductase deficiency	Dysgenetic gonad
Laboratory Marker	Elevated 17-hydroxy progesterone Serum electrolytes		Normal	Increased T:DHT ratio (testosterone to dihydrotestosterone)	*Decreased basal testosterone *Decreased AMH *Minimal or no elevation of testosterone on hCG stimulation test
Gonad	Ovaries	Ovotestis/testis	Testis	Testis (inguinal/labial/scrotal)	Testis on one side and streak gonad on other side
Uterus/Müllerian structures	Present	Present	Absent	Absent	Rudimentary uterus present with fallopian tube on the side of the streak gonad

Abbreviations: AMH, anti-Müllerian hormone; CAH, congenital adrenal hyperplasia; DHT, dihydrotestosterone; DSD, disorders of sex development; hCG, human chorionic gonadotropin.

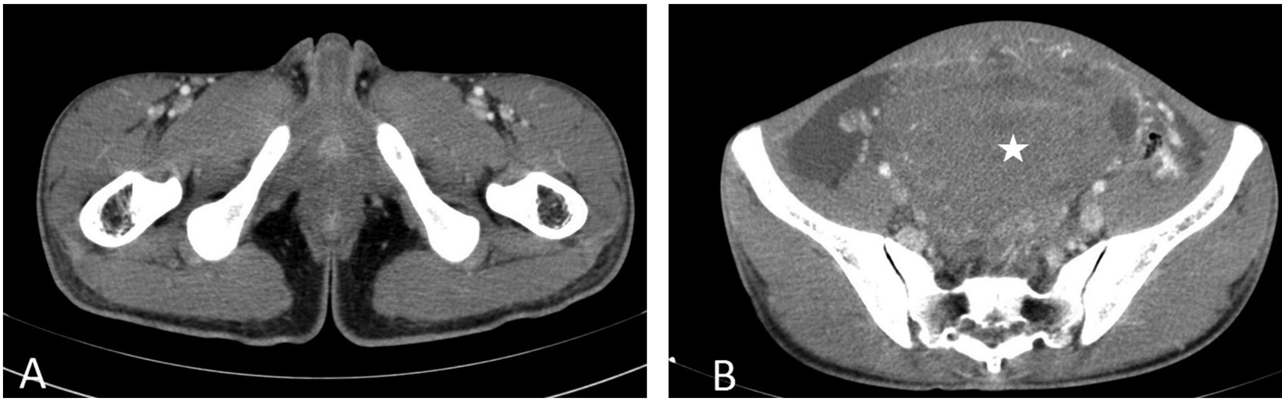

Fig.16 A 21-year-old lady with ambiguous genitalia, primary amenorrhea and abdominal distension. Computed tomography images (**A**, **B**) show enlarged phallus and a large, heterogeneously enhancing mass (*) in lower abdomen that was confirmed to be dysgerminoma.

choriocarcinoma with less favorable prognosis.[24] Hence, gonadectomy is indicated. On imaging, echogenic foci within the gonad located in the inguinal region or in an intraabdominal location may indicate presence of gonadoblastoma, as these tumors can calcify.[4,5]

Conclusion

Imaging has a role in the evaluation of DSD. It helps to locate and identify gonads, to look for the presence of Müllerian structures and thus contributes to the process of assigning the right gender to the individual. In disorders with an increased risk of malignancy, imaging is needed to locate and plan gonadectomy. A multidisciplinary approach is needed for the management of DSD.

Conflict of Interest
None declared.

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