Fertility Issues in Disorders of Sex Development

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KEYWORDS

• Aromatase • Gonadal dysgenesis • Ovotestis • Hypospadias • Müllerian remnants • Ambiguous genitalia • Androgens • AMH

KEY POINTS

- Fertility potential in patients with disorders of sex development is influenced by specific factors related to the causal disorder, and general functional and anatomic features, irrespective of the etiology.
- In patients with testicular dysgenesis, severe forms are raised as females, and motherhood might be possible with hormone replacement and oocyte donation.
- In patients with specific defects of androgen synthesis or action, the absence of uterus and Fallopian tubes hampers motherhood.
- In some virilized 46,XX patients raised as females, fertility is possible after adequate hormonal and surgical treatments.
- Patients raised as males are most frequently oligospermic or azoospermic, with the exception for milder forms, where full spermatogenesis can be achieved spontaneously or after hormonal treatment.

INTRODUCTION

Fertility potential should be considered by the multidisciplinary team when addressing gender assignment, surgical management, and patient and family counseling of individuals with disorders of sex development (DSD) (**Box 1**).

DSD refers to all congenital conditions in which the development of chromosomal, gonadal, or genital sex is atypical.[1] Here we address fertility issues in DSD conditions

Disclosure Statement: The authors have nothing to disclose.

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Endocrinol Metab Clin N Am 44 (2015) 867–881
http://dx.doi.org/10.1016/j.ecl.2015.07.012 **endo.theclinics.com**

Box 1
Factors that might influence fertility potential in patients with disorders of sex development (DSD)

- Specific factors related to the etiology
- Factors found in most DSD, irrespective of the etiology:
  - Functional and/or anatomic features
  - Features related to the management and/or the surgical corrections

affecting the normal pathway of gonadal and/or genital sex differentiation during intrauterine life (Fig. 1). Not discussed are reproductive outcomes in Klinefelter syndrome, Turner syndrome, and congenital adrenal hyperplasia due to 21-hydroxylase deficiency, which are discussed elsewhere in this issue.

46,XY DISORDERS OF SEX DEVELOPMENT

In 46,XY individuals, defects of gonadal differentiation (dysgenetic DSD) or in androgen or anti-Müllerian hormone (AMH) synthesis or action result in incomplete or absent masculinization (see Fig. 1). According to the severity of the defect, patients might present with female, ambiguous, or minimally undervirilized external genitalia (micropenis and cryptorchidism).[2] Fertility potential in these patients should be analyzed considering clinical form (or severity of the condition) and sex assignment.

Complete Forms of 46,XY Disorders of Sex Development

Severe gonadal dysgenesis or absent androgen synthesis or action result in female external genitalia. Affected individuals always reared as girls have no possibility for spontaneous fertility because of the lack of oocytes, but pregnancy might be achieved in dysgenetic DSD, owing to the persistence of Müllerian remnants (Fig. 2A), with the use of allogenic oocytes (Table 1).[3,4]

In defects of androgen synthesis or action, Müllerian structures are generally absent (see Fig. 2B). Sporadic cases with presence of minimal Müllerian remnants have been reported,[5,6] but their functionality for embryo implantation has not been reported at present. Nonetheless, the first case of a live birth following uterine allograft transplantation has recently been reported in a patient with congenital absence of the uterus (Rokitansky syndrome),[7] thus opening a promising alternative.

Partial forms of 46,XY Disorders of Sex Development

Partial forms result in a broad phenotypic spectrum, from genital ambiguity to complete virilization in individuals presenting with infertility (see Table 1). Depending on the degree of undervirilization of the genitalia, female or male sex of rearing might be possible. For affected patients assigned female, considerations regarding fertility are similar to those discussed for the complete forms.

Fertility in patients raised males might be affected by impaired spermatogenesis secondary to gonadal dysgenesis and/or androgen deficiency, cryptorchidism, anatomic defects of the male reproductive tract (eg, perineoscrotal hypospadias, defects of the epididymis or vas deferens), or complications of genitourinary surgery. Unfortunately, for most patients with DSD reported in infancy or childhood, information regarding pubertal development and/or fertility is not available.

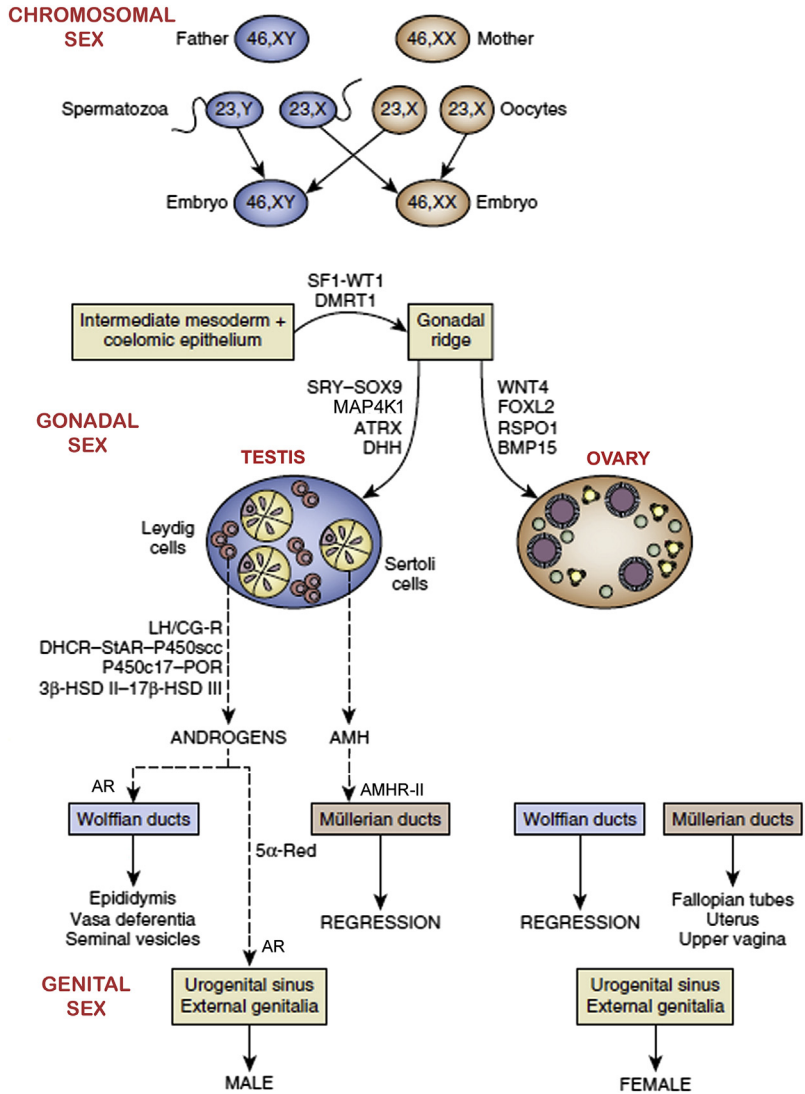

Fig. 1. The 3 stages in normal sexual differentiation. (1) Chromosomal sex is determined by the sex chromosome (X or Y) present in the spermatozoon at fertilization. (2) Gonadal sex differentiation occurs after the sixth week of embryonic life, when the indifferent gonadal ridge takes the testicular or the ovarian pathway, according to the gene expression pattern. (3) Sex of the internal and external genitalia depends on the secretion and action of 2 testicular hormones: testosterone, by Leydig cells, and AMH, by Sertoli cells. Male genital differentiation occurs when androgens (testosterone and DHT) and AMH are present and act through their respective receptors, the AR and AMH type II receptor (AMHR-II). Female differentiation takes place in their absence. (*From* Rey RA, Josso N. Diagnosis and treatment of disorders of sexual development. In: Jameson JL, De Groot LJ, de Kretser D, et al, editors. Endocrinology: adult and pediatric. 7th edition. Philadelphia: Elsevier Saunders; 2015. p. 2086–118; with permission.)

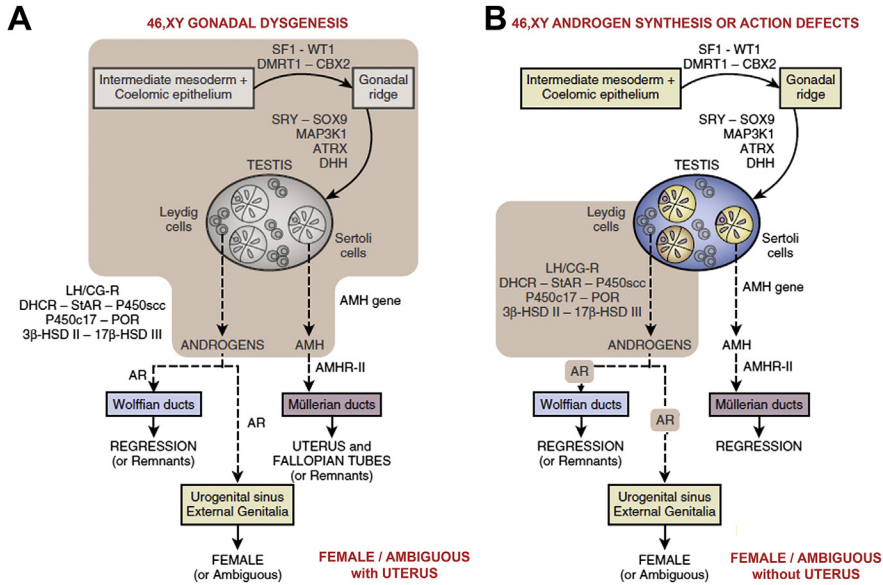

Fig. 2. Pathogenesis of 46,XY DSD. (*A*) Dysgenetic DSD results from defects in testicular differentiation from the gonadal ridge. Both testicular hormones are defective: androgen deficiency results in underdevelopment or complete regression of Wolffian ducts and feminization of the urogenital sinus and external genitalia, whereas AMH deficiency results in the development of the uterus and Fallopian tubes. (*B*) Androgen synthesis defects results from Leydig cell specific dysfunction, whereas androgen action defects results from AR mutations. AMH action is present in both conditions, resulting in Müllerian duct regression. (*From* Rey RA, Josso N. Diagnosis and treatment of disorders of sexual development. In: Jameson JL, De Groot LJ, de Kretser D, et al, editors. Endocrinology: adult and pediatric. 7th edition. Philadelphia: Elsevier Saunders; 2015. p. 2086–118; with permission.)

Testosterone is essential to maintain spermatogenesis and male fertility acting through classical and nonclassical signaling pathways.[8] In the absence of androgen synthesis or action, spermatogenesis rarely progresses beyond meiosis, the blood–testis barrier development is compromised, immature germ cells are prematurely detached from Sertoli cells, and full spermatogenesis cannot be achieved.[8]

Persistently cryptorchid testes might contribute to the decrease in germ cell number.[9] However, considering the primary disorder in these patients, the management of the position of the gonads does not appear to change the reproductive outcome.

Male genitoplasty usually includes chordee correction and penile straightening, urethroplasty, glanuloplasty, correction of scrotal deformities, and orchiopexy. Ejaculation disorders have been reported in adulthood.[10] However, very few studies have evaluated the long-term outcomes,[11–13] and progressive changes in surgical techniques warrant the performance of new studies.

Despite the considerations listed previously, fertility and fatherhood have been reported in a few patients with 46,XY DSD raised as males with milder forms of gonadal dysgenesis or defects in androgen synthesis or action (see **Table 1**).

Partial gonadal dysgenesis

In testicular dysgenesis, germ cells are the most affected cell population, usually leading to incomplete spermatogenesis and increased risk of germ cell tumors.[14] Pubertal

Table 1
Fertility issues in patients with 46,XY disorders of sex development (DSD)

DSD Etiology	Fertility
1. Gonadal dysgenesis • Yp deletions, Xp duplications (DSS), 9p deletions (involving *DMRT1/DMRT2*) • Mutations of genes involved in testicular differentiation: *SRY, SOX9, SF1, WT1, ATRX, DHH, MAP3K1*.	*Severe forms:* raised as females, motherhood possible with hormone replacement and oocyte donation *Milder forms:* raised as males, azoospermia/oligospermia, very rarely spontaneous fatherhood
2. Defects of androgen production • LHCG receptor mutations • Inborn errors of testosterone Biosynthesis: Mutations of StAR, P450scc, P450c17, POR, 3β-HSD, 17β-HSD	*Severe forms:* raised as females, motherhood impossible due to absence of uterus *Milder forms:* raised as males, azoospermia, more rarely fatherhood spontaneous or after hormonal treatment
3. Defects in androgen target organs	
DHT deficiency	*Severe forms:* raised as females, motherhood impossible due to absence of uterus *Milder forms:* raised as males, or changing from female to male gender at puberty, fatherhood possible spontaneously or after hormonal treatment
Androgen insensitivity	*Complete:* Raised as females, motherhood impossible due to absence of uterus *Partial/Mild:* azoospermia/oligospermia, fatherhood possible in rare cases after hormonal treatment
4. Persistent Müllerian duct syndrome • AMH mutations • AMH Receptor mutations	Azoospermia, probably due to long-standing cryptorchidism, or damage of epididymis, vas deferens or testicular blood supply at surgery

Abbreviations: AMH, anti-Müllerian hormone; DHT, dihydrotestosterone; DSS, dosage sensitive sex reversal; HSD, hydroxysteroid dehydrogenase; LHCG, luteinizing hormone/chorionic gonadotropin; POR, P450 oxidoreductase; P450scc, cholesterol side-chain cleavage enzyme; StAR, steroidogenic acute regulatory protein.

development among these patients may be partial, requiring testosterone replacement, but there are also reports on complete pubertal development.[15–17] Most patients are infertile, but there is a huge variability even within the same family. One example is a kindred of four 46,XY individuals with a mutation in *NR5A1*, encoding SF1: all presented with hypospadias at birth; although only one of them also had micropenis and cryptorchidism, the other 3 developed normally, and one fathered 5 children.[16] Another example is related to a mutation in *MAP3K1*, involved in the testicular differentiation pathway: a man with hypospadias and chordee was fertile and fathered 2 children. The father and both children had different degrees of 46,XY gonadal dysgenesis.[18]

Partial androgen synthesis defects

Luteinizing hormone receptor Leydig cell hypoplasia is a rare condition that results from inactivating homozygous or compound heterozygous mutations of the luteinizing hormone–chorionic gonadotropin receptor (LHCGR) in 46,XY subjects. Mild phenotypes have predominantly male external genitalia with micropenis and/or hypospadias

or hypergonadotropic hypogonadism without genital ambiguity. Generally these patients are oligospermic and infertile.[12] Successful testicular sperm recovery and fertility have been reported in 2 males (see **Table 1**).[19,20]

Steroidogenic acute regulatory protein and cholesterol side-chain cleavage Defects in the early steps of steroidogenesis include mutations in the steroidogenic acute regulatory protein (StAR) or the cholesterol side-chain cleavage (P450scc) enzyme.[21–23] In late-onset "nonclassical" forms, secondary to mutations that retain partial activity, affected individuals show a broad phenotypic spectrum including normal pubertal development and adult sexual function.[22,24,25] Even though the adult phenotype is indicative of potentially compromised reproductive outcome in many patients, fertility has been reported.[26]

Cytochrome P450c17 Cytochrome P450c17, through its 17α-hydroxylase/17,20-lyase activities, is needed for cortisol and testosterone synthesis. Most of the patients with P450c17 deficiency have been reared as female, and data of patients raised as male are lacking.[21,23] In isolated 17,20-lyase deficiency individuals with 46,XY DSD raised as males usually showed primary hypogonadism requiring testosterone replacement.[27] Fertility has not been reported.

P450 oxidoreductase Mutations in P450 oxidoreductase (POR) cause a complex steroidogenic spectrum including partial P450c17, aromatase (P450C19), and 21-hydroxilase (P450c21) deficiencies.[22,23] The clinical phenotype is remarkably variable and may include skeletal malformations evocative of the Antler–Bixler syndrome.[22,23,28,29] POR deficiency affects genital differentiation in both sexes. Mildly affected male individuals may present with normal or delayed pubertal progression and biochemical signs of compensated hypogonadism. Even though fertility has not been reported, the capacity for spontaneous pubertal development in affected boys justifies a primarily watchful-waiting approach to the evaluation of reproductive outcome.[30] Furthermore, because a 46,XX patient with POR deficiency has been described as a phenotypically normal woman with infertility,[31] it is possible that many XX and XY patients with mild forms of POR deficiency may remain undiagnosed.

3β-hydroxysteroid dehydrogenase type 2 Deficiency of 3β-hydroxysteroid dehydrogenase type 2 (3β-HSD2) impairs steroidogenesis in the adrenals and gonads, leading to glucocorticoid and mineralocorticoid deficiency and ambiguous genitalia. Spontaneous pubertal development has been reported[21–23,32] and it has been suggested that pubertal levels of gonadotropins may increase the expression and activity of type I 3β-HSD in the gonad.[33] Whereas spermatogenic arrest[34] and azoospermia[32] have been observed, a 34-year-old man with adequate spermatogenesis has fathered 2 children.[35] Testicular adrenal rests might compromise fertility in this condition.

17β-hydroxysteroid dehydrogenase type 3 Deficiency of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) is a male-limited disorder affecting testicular conversion of androstenedione to testosterone. Patients with 46,XY with mild forms of 17β-HSD3 deficiency may virilize on their own at puberty.[36] High LH levels enforce testosterone synthesis and the activity of other peripheral 17β-HSD enzymes may also contribute to pubertal virilization. Nevertheless, in adulthood insufficient intratesticular testosterone levels lead to impaired spermatogenesis and azoospermia.[21–23]

5α-reductase type 2 Dihydrotestosterone (DHT) is the main androgen driving the masculinization of the urogenital sinus and external genitalia; however, DHT appears

not to play a major role in spermatogenesis. The classical pathway of DHT synthesis involves the action of 5α-reductase type 2 (5α-RD2) in genital skin.[37,38] Affected patients show ambiguous genitalia with hypospadias and cryptorchidism. At puberty, spontaneous virilization occurs. Adult patients report male libido and sexual activity; however, small penis size may impair normal intercourse. Semen analysis is characterized by extremely low volume, increased viscosity, and poor liquefaction, attributed to rudimentary prostate glands and small seminal vesicles.[39,40] Most of the affected individuals are infertile, although spontaneous proven fertility was reported in 2 brothers born with ambiguous genitalia from a Swedish family.[41] In other cases, in vitro fertilization using the patients' sperm cells resulted in successful pregnancies,[38,40] providing support for raising these individuals as males.

AKR1C2/AKR1C4 The alternative pathway of DHT synthesis, found in the human fetal testis and needed for normal male sexual differentiation, involves the AKR1C2 and AKR1C4 enzymes.[23] Recently, compound heterozygous mutations in both genes have been found in families with 46,XY DSD. Even though data regarding age and pubertal status are unknown, one of the patients reported appears to be fertile.[42]

Androgen receptor Androgen receptor (AR) mutations causing partial forms of androgen insensitivity (PAIS) result in a variable phenotypic spectrum, ranging from genital ambiguity to male infertility, a condition known as mild AIS (MAIS).[43] In addition to its effects on gametogenesis, some patients have defects in Wolffian duct derivatives, such as absence or hypoplasia of the vas deferens that might affect reproduction. At present, although challenging, fertility is possible for individuals with PAIS who are raised male.[44–48] In some cases, fertility was spontaneous,[46,47] whereas in others, oligospermia was corrected and the sperm count was restored following high-dose androgen treatment (see **Table 1**).[45]

Anti-Müllerian hormone/anti-Müllerian hormone receptor 2 Defects in testicular AMH production, as well as AMH receptor defects, drive to the same form of internal genital defects in otherwise normally virilized male individuals: the persistent Müllerian duct syndrome (PMDS). The existence of a uterus and Fallopian tubes is an unpredicted finding in boys undergoing surgery for cryptorchidism associated or not with inguinal hernia. Leydig cell androgen production is normal, but azoospermia is common due to the long-standing abnormal position of the gonads or to damage of testicular blood supply during surgical procedures.[49]

46,XX DISORDERS OF SEX DEVELOPMENT

In 46,XX fetuses (**Fig. 3**), virilization along with normal ovarian organogenesis is caused by excessive exposure to androgens of fetal and/or maternal origin (**Table 2**). Virilization can also reflect the existence of testicular tissue: ovotesticular and testicular DSD, which are discussed separately (**Table 3**).

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia due to mutations in the *CYP21A2* gene causing 21-hydroxylase deficiency (21OHD) is the most common cause of DSD in 46,XX infants, and is discussed elsewhere in this issue.

With the exception of 21OHD, information on postpubertal gonadal function and adult reproductive outcome and fertility in 46,XX DSD with normal ovarian organogenesis is scarce.

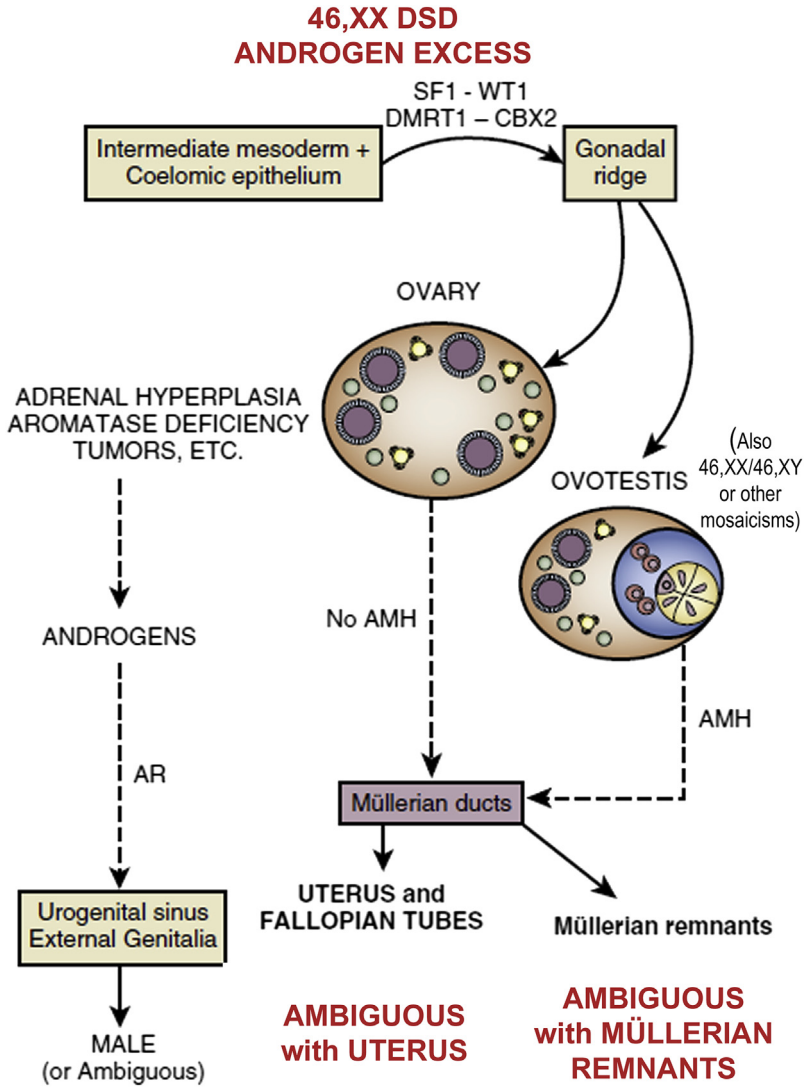

Fig. 3. Pathogenesis of 46,XX DSD. Androgen excess may derive from abnormal adrenal function (congenital adrenal hyperplasia), aromatase deficiency or androgen-secreting tumors in 46,XX fetuses with normal ovarian development. Alternatively, ovotestes can develop in 46,XX individuals with or without SRY, and also in individuals with 46,XX/46,XY or other mosaicisms carrying a Y chromosome. In patients with ovotesticular DSD, the presence or absence of Müllerian remnants depends on the amount of testicular tissue secreting AMH. (*From* Rey RA, Josso N. Diagnosis and treatment of disorders of sexual development. In: Jameson JL, De Groot LJ, de Kretser D, et al, editors. Endocrinology: adult and pediatric. 7th edition. Philadelphia: Elsevier Saunders; 2015. p. 2086–118; with permission.)

Table 2
Fertility issues in 46,XX disorders of sex development (DSD) due to exposure to excessive androgens

DSD Etiology	Fertility
Congenital adrenal hyperplasia • 21-hydroxylase deficiency • 11β-hydroxylase deficiency • 3β-HSD deficiency • POR deficiency	*Classic forms:* raised as females: fertility possible if adequate hormonal and surgical treatments
Aromatase deficiency	Unknown

Abbreviations: HSD, hydroxysteroid dehydrogenase; POR, P450 oxidoreductase.

11β-hydroxylase

11β-hydroxylase deficiency (11OHD) due to mutations in the *CYP11B1* gene is a rare form of congenital adrenal hyperplasia. In classic forms, newborns are virilized like in 21OHD, but mineralocorticoid activity is not deficient due to the accumulation of 11-deoxycortisol and 11-deoxycorticosterone. Despite multiple publications on 11OHD, data about fertility are scarce. Only one successful pregnancy in one properly treated woman has been reported.[50] Caution should be taken for sexually active women who attempt pregnancy because spironolactone, used for hypertension management, is potentially teratogenic.[51]

3β-HSD2

Like 21OHD and 11OHD, 3β-HSD2 deficiency virilizes the 46,XX fetus; however, the androgen excess is less severe, and genital surgery is rarely required.[51] As the girl grows, however, the main problems are due to androgen excess and hypogonadism. Deficiency of 3β-HSD2 might variably affect normal ovarian estrogen synthesis. Regular menses and evidence of progesterone secretion have been described in one female individual with the classic form of the disease; however, there is no information on fertility.[52]

P450 oxidoreductase

Subjects with 46,XX and POR deficiency present with partial in utero virilization without postnatal progression. This is the result of at least 2 mechanisms: partial placental aromatase deficiency and androgen biosynthesis through the fetal alternative steroidogenic pathway.[22,29,30,51] The relative contribution of each mechanism varies with the different POR mutations involved. Affected patients generally present with complete absence of puberty, but partial and even complete pubertal development have been reported.[30,31] The disruptive impact of mutant POR on sterol synthesis and metabolism might contribute to ovarian cyst development in addition to high gonadotropin levels resulting from estrogen deficiency. CYP51A1 requires electron transfer from POR for catalytic activity and catalyzes the conversion of lanosterol to meiosis-activating sterols (MAS). Follicular fluid MAS has been shown to be crucial for the resumption of oocyte meiosis at puberty and also support oocyte maturation.[30] Fertility has never been reported.

Aromatase Deficiency

Aromatase (P450arom) deficiency is a rare form of 46,XX DSD due to fetoplacental androgen excess. Aromatase catalyzes the synthesis of estrogens from androgens.

In postnatal life, the effect of excessive androgens and insufficient estrogens is responsible for a variable clinical picture. In complete forms, affected female individuals are born with ambiguous genitalia and progress to hypergonadotropic hypogonadism with pubertal delay, primary amenorrhea, and hyperandrogenism. Some patients develop enlarged ovaries and large ovarian cysts, sometimes requiring surgical removal for torsion, pain, or bleeding. Those factors, along with surgical consequences of genital reconstruction, might affect reproduction in these women. Variable phenotypes have been described and some affected female individuals have spontaneous breast development and uterine growth despite androgen excess and virilization.[53–55] However, information about the course of the disease in adulthood and long-term consequences on fertility is unknown. Data on the long-term follow-up of these patients might clarify our understanding of the reproductive outcomes.

Management of Fertility Issues

In 46,XX DSD due to exposure to excessive androgens, the focus and goals of treatment change as the patient grows and becomes an adult when reproduction may become a concern.

Assisted reproduction might be an alternative to offer to women who cannot spontaneously conceive. In some conditions, adequate clinical and surgical management during infancy and childhood might anticipate the long-term complications, as seen in 21OHD and 11OHD CAH.

OVOTESTICULAR AND TESTICULAR DISORDERS OF SEX DEVELOPMENT

Ovarian differentiation is the normal pathway in 46,XX fetuses (see **Fig. 1**). However, testicular tissue may differentiate in fetuses with 46,XX/46,XY or other Y-bearing mosaicisms or in 46,XX individuals with translocations of Yp carrying the *SRY* gene; interestingly, testicular tissue can also develop in 46,XX fetuses devoid of *SRY*.[56] Testicular tissue can exist together with ovarian tissue, a condition known as ovotesticular DSD (previously called true hermaphroditism, see Ref.[1], or as the only gonadal tissue, a condition known as 46,XX testicular DSD, previously named XX male, see Ref.[1]). In patients carrying SRY, the underlying pathophysiology is easily understood (see **Fig. 1**), whereas in 46,XX SRY-negative patients, recent studies have unveiled defects in potentially antitesticular genes, like *RSPO1*,[57] and overexpression of protesticular genes, like *SOX9*[58] and *SOX3*.[59]

Table 3
Fertility issues in 46,XX testicular disorders of sex development (DSD) and in ovotesticular DSD independently of the karyotype

DSD Etiology	Fertility
46,XX Testicular DSD	Raised as males: azoospermia due to the existence of 2 X chromosomes and absence of Y chromosome
Ovotesticular DSD	Raised as females: pregnancy possible spontaneously or following the use of ART with the patient's own oocytes. Raised as males: azoospermia/oligospermia, very rarely fatherhood spontaneously or after ART (TESE + ICSI)

Abbreviations: ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; TESE, testicular sperm extraction.

Ovotesticular Disorders of Sex Development

The diagnosis of ovotesticular DSD is histologic and requires the existence of seminiferous cords and ovarian follicles with oocytes. The most prevalent karyotype is 46,XX, but 46,XX/46,XY or other mosaicisms also can occur (see **Fig. 3**). The degree of virilization depends on the amount of functional testicular tissue. The ovarian tissue usually develops more normally than the testicular portion. Therefore, the preservation of ovarian tissue at surgery in patients raised as females may be of major importance for the achievement of pregnancy, either spontaneous or following the use of assisted reproductive techniques with the patient's own oocytes. To date, there are fewer than 15 cases of pregnancy reported in patients with ovotesticular DSD raised as females; most of them have had complications, for example, preterm labor or morbidity related to the delivery process, due to the female reproductive tract defects.[60] For patients raised as males, the considerations are similar to those previously described for 46,XY partial dysgenesis. A successful intracytoplasmic sperm injection (ICSI) procedure with subsequent live birth has been reported after testicular sperm extraction from a 46,XX/46,XY azoospermic male patient.[61]

46,XX Testicular Disorders of Sex Development

Most patients with this condition have normal male genitalia, but cases with genital ambiguity also have been reported. Like patients with Klinefelter syndrome, XX males have normal testicular function until midpuberty, with spontaneous progression of secondary sex characteristics.[62] However, the existence of 2 X chromosomes and the absence of a Y chromosome drive to germ cell degeneration, small testes, and azoospermia.[63]

SUMMARY

As patients with DSD grow and become adults, reproduction arises as an important issue. The establishment of a multidisciplinary team facilitating close interaction among the pediatrician, adult endocrinologist, gynecologic/urologic surgeon, fertility specialist, and clinical psychologist with experience in these conditions is mandatory for the long-term follow-up and the achievement of an integrated approach to the patient.

A better characterization of the more recently described conditions and detailed information about the long-term follow-up of patients with DSD reported in infancy or childhood is important to address the lifelong consequences, as in other chronic medical conditions.

Assisted reproduction might be an alternative to offer to those who cannot spontaneously conceive.

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