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

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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.