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Review Article

Fertility in disorders of sex development: A review

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Summary

Introduction
Disorders of sex development (DSD) are a heterogeneous group of complex conditions that can affect chromosomal, gonadal, and/or phenotypical sex. In addition to impacts on internal and external genitalia,these conditions can affect fertility potentialto various degrees. In this review we discuss fertility issues including gonadalpreservation and reproductive outcomes based on specific DSD conditions.

Methods and Materials
A systematic literature review was performed on Embase™, PubMed®, and Google Scholar™ for disordersof sex development and infertility. Original research articles and relevant reviews were examinedand a synopsis of these data was generated for a comprehensive review of fertility potential in disorders of sex development.

Results
While patients with some DSDs may have functioning gonads with viable germ cells but an inability to achieve natural fertility secondary to incongruent internal or external genitalia, other patients may have phenotypically normal genitalia but infertility due to abnormal gonad development. Fertility rates in females with congenital adrenal hyperplasia (CAH) depend on phenotype and are inversely proportionalto the severity of the disease. Men with classic CAH have reduced fertility and due to the presence of testicular adrenal rest tumors and to suppression of the hypothalamic-pituitary-gonadal axis by high systemic levels of androgens. Infertility is seen in complete androgen insensitivity and subfertility is common in partial cases. Fertility is rare in pure or mixed gonadal dysgenesis, ovotesticular disorder, Klinefelter syndrome, and XX males.

Conclusion
Fertility potential appears to be the highest in patientswith XX or XY CAH, especially non-classic forms. Advancements in assisted reproduction techniques has in rare cases produced offspring in some diagnoses thought to be universally infertile. Discussion of fertility issues with the patient and family is essential to the optimal treatment of each patient and an important part of the multi-disciplinary approach to evaluating and counseling these families.

Introduction

Disorders of sex development (DSD) include a wide variety of congenital conditions in which the development of chromosomal, gonadal, or phenotypical sex is atypical [1]. Given the complexity of these conditions, the pediatric urologist and entire multidisciplinary team need to consider many issues when counseling families about gender assignment, need for and timing of medical or surgical intervention, and long-term outcomes. In particular, an understanding of fertility potential is essential to these discussions, and is often a central concern for the parents of an individual with DSD. This review examined fertility issues, including gonadal preservation and reproductive outcomes, based on specific DSD conditions (see Table 1).

Fertility in various forms of disorders of sex development

46,XX DSD (masculinized female)

Congenital adrenal hyperplasia (CAH) is the most common cause of the masculinized female and ambiguous genitalia at birth. Classic CAH is due to a 21-hydroxylase deficiency and is the most common sub-type. Fertility rates in females with CAH depend on phenotype and are inversely proportional to the severity of the disease. Overall, women with CAH have decreased fertility rates, with infertility most likely in classic salt-wasting CAH and CAH due to 11β-hydroxylase deficiency. Fertility is more frequent with simple masculinizing CAH and most likely in non-classic CAH (due to

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Table 1 Fertility summary in DSD.

Type of DSD	References	Fertility rate	Overall fertility and specifics
46,XX DSD (masculinized female)			
CAH			
21-hydroxylase deficiency			**Reared female**: fertility possible with hormonal replacement/treatment. Fertility rates: non-classic > simple masculinizing > classic salt wasting
Classic salt-wasting CAH	Claahsen-van der Grinten et al. [4]	0—10%	
Simple masculinizing CAH	Claahsen-van der Grinten et al. [4]	33—50%	
Non-classic CAH	Claahsen-van der Grinten et al. [4]	63—90%	
11β-hydroxylase deficiency	Simm et al. [7]	1 case report	Subfertility: rare fertility with hormonal therapy
3β-HSD deficiency		No reported cases	Infertile to date
CYP17A1 mutation	Marsh et al. [9], Levran et al. [10]	1 case report	Infertile: 1 case with IVF and frozen ET
46,XY DSD (undermasculinized male)			
CAH			
21-hydroxylase deficiency	Falhammar et al. [12]	~1/2 compared to national data controls	Fertility reduced in males; lower T/E2 ratio, higher FSH; abnormal semen parameters in ~50%; TARTs may play role and are treated with steroids
CLAH	Metherell et al. [15]	Cases reported	*Classical form* leads to complete sex reversal (infertile); *non-classical forms* with varied phenotype, fertility reported in males (subfertile)
3β-HSD deficiency	Burckhardt et al. [16]	1 case report	Subfertile to infertile; testicular biopsies show spermatogenic arrest and Sertoli-only cells
POR deficiency	Fukami [17]	No reported cases	Infertile: delayed puberty common
Disorders of T biosynthesis			
17OH deficiency	Diamond and Yu [18]	No reported cases	*Complete form* often reared female with gonadectomy and estrogen replacement at puberty (infertile); *Partial form* require T replacement at puberty if reared male (infertile)
17 β-HOR deficiency	Auchus and Miller [19]	No reported cases	Infertile
Leydig cell hypoplasia/ agenesis	Bakircioglu et al. [20]	1 case report	Infertility thought universal with azoospermia common; recently 1 case of life birth after ICSI with cryopreserved sperm from micro-TESE
Disorders of androgen target tissue			
Androgen insensitivity syndrome			
Complete AIS	Rutgers and Scully [21]	No reported cases	**Reared female**: absence of Müllerian structures (infertile); possibility of male fertility factor low
Partial AIS	Tordjman et al. [24]	Cases reported	**Reared female**: absence of Müllerian structures (infertile); **Reared male**: variable phenotypes and typical cryptorchidism histology; fertility possible spontaneously (hormonal treatment) or with IVF (subfertile)
Disorders of T metabolism			
5α-reductase type 2 deficiency	Katz et al. [29], Kang et al. [30]	Decreased	**Reared female**: gonadectomy to prevent virilization (infertile); **Reared male or male gender reassignment at puberty**: orchiopexies and have oligoasthenoteratospermia, natural paternity rare but fertility possible with IUI and TESE/ICSI

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