DSD in Boys: Impact on Fertility

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Abstract

Differences or disorders of sex development (DSD) include various congenital conditions in which chromosomal, gonadal, or anatomical sex development is atypical. The incidence varies according to the category of DSD but the total incidence is high if hypospadias and undescended testes are included. Fertility prospects may be a concern for DSD patients and their parents. With the development of modern medical technologies and treatment opportunities, fertility diagnostics, information, and treatment have changed. Assisted reproductive technology has developed during the past decades and has become more available with an improving success rate. Intracytoplasmic sperm injection and testicular sperm retrieval, have further improved the possibilities for men with DSD to become biological parents. Some studies have determined the presence of germ cells in the gonads of patients with DSD suggesting that the potential for fertility may be higher than previously thought. However, fertility outcomes among individuals with DSD have not been fully investigated. Moreover, previous study showed that information on fertility problems and treatment possibilities given to patients with DSD needs to be improved. The use of registries to study fertility outcomes is essential for a better knowledge of fertility in patients with these rare conditions.

Key words: Disorders sexual development, DSD, fertility, hypospadias, androgen insensitivity, PMDS, androgens, cryptorchidia, testis

Introduction

Differences or disorders of sex development (DSD) include various congenital conditions in which chromosomal, gonadal, or anatomical sex development is atypical [1].

The overall incidence of DSD depends on how it is defined. In the newborn period, 1 in 200 to 300 births will have atypical genitalia and over 70% of these will have hypospadias [2]. In about 1 in 3000 births, the atypical genitalia require specialist input and in about one in 11,000 cases, the genitalia are so atypical that sex assignment is delayed beyond birth [3].

Fertility can be impaired in people with different forms of DSD due to anatomical or biological causes inherent in the disease. In addition, fertility can also be affected following the surgical or medical treatments to which they are subjected throughout their follow-up.
Fertility possibilities may be an important concern for DSD patients and their parents. Better knowledge of their fertility potential is essential to improve the treatment and long-term management of the pathology and provide them with adequate psychosocial and medical support.
Fertility preservation methods (storage of oocytes, sperm or precursor reproductive tissues for future use) and societal perceptions have evolved considerably in recent years, so that having a biological child is now possible for a significant proportion of adults with DSD.
Fertility possibilities differ depending on the type of DSD.
In this review we aim to assess fertility outcomes and issues in boys with different forms of DSD, based on data from European registries after a focus on specific conditions.

Conditions leading to DSD in boys

Embryologically, gonadal sex determination occurs during week 7 of gestation. Expression of the sex-determining region Y (SRY) gene results in differentiation of the bipotential gonad into a testis, differentiation of Wolffian structures (males), and regression of Mullerian structures (females).

The development of the external genitalia and the urethral plate from the genital tubercle begins at the 8th week of gestation. Tubercle elongation continues from weeks 11 to 16, with fusion of the urethral folds to create the penile urethra. The full formation of the male external genitalia comes at week 20 under the influence of testosterone and dihydrotestosterone. Spermatogenesis is initiated by genes located on the long arm of the Y chromosome. Sperm maturation is facilitated by the action of pituitary gonadotropins, stimulating the production of testosterone by Leydig cells and the production by Sertoli cells of the androgen-binding protein to transport testosterone across the blood-testis barrier.

All of these steps are essential for proper development and condition the achievement of well-developed male genitalia. A perturbation of any of these steps may lead to DSD.

Focus on specific conditions

Disorder of gonadal development

Klinefelter syndrome is the most common chromosomal cause of abnormal sex differentiation and is characterized by males with at least one Y chromosome and at least two X chromosomes. It is most commonly seen in adolescence in a context of delayed puberty, or in adulthood faced with infertility [4]. Despite the fact that the majority of them have azoospermia, fertility has been shown to be possible with the use of Testicular sperm extraction (TESE) followed by intracytoplasmic sperm injection (ICSI). The success rate of sperm retrieval in these men reaches 40 to 66% [5].

46,XY partial gonadal dysgenesis (PGD) results in varying degrees of external virilization and the presence of a uterus or uterine remnants. In severe forms, patients are infertile (azoospermia), but in some cases such as SF-1/NR5A1 mutations, variable testicular function and viable sperm are observed [6].

Sex chromosome mosaicism, such as 45X/46XY, may appear with atypical genitalia. Patients may present hypospadias, abnormal scrotum, cryptorchidism, and micropenis [7]. The gonads

are generally devoid of germ cells thus impacting fertility [8] but in some cases TESE can be performed [9].

Ovotesticular DSD (OT) is defined as the situation in which both ovarian and testicular tissue are present, regardless of karyotype. The development of external genitalia and internal structures depends on the hormonal function of the testicular part of the gonad(s). The testis or testicular component of the ovotestis may have normal endocrine function but will have few normal germ cells and scanty sperm [10]. Successful paternity has been reported after TESE and ICSI using sperm from a man with ovotesticular DSD [11].

In XX males with SRY translocation on one X chromosome, the rest of the Y chromosome is no longer present. These men may have micropenis, cryptorchidism and hypospadias, but infertility and azoospermia are the most characteristic, secondary to the absence of the rest of the Y chromosome [12].

Disorder of androgen synthesis

Defects in androgen biosynthesis, such as 17b-hydroxysteroid dehydrogenase type 3 and 5a-reductase type 2 deficiency, result from enzymatic defects in the steroidogenesis pathway. They lead to varying degrees of undermasculinization depending on the enzyme deficiency. These individuals have often been raised as girls, but if the testicles are preserved, they will virilize during puberty due to isoenzyme activation [13].

17-beta hydroxysteroid dehydrogenase type 3 (17βHSD-3) is primarily presented in the testes and converts androstenedione to testosterone, which is required for normal masculinization of the external genitalia in utero.

5-a-reductase deficiency (5ARI) is a disorder of the enzyme five-alpha reductase, which plays a vital role in the conversion of testosterone to dihydrotestosterone. Patients with 5ARI have a 46,XY karyotype with male internal sexual structures (seminal vesicles, epididymis, ejaculatory ducts, and vas deferens) and testes, but have atypical external genitalia. 5ARI deficiency is also associated with hypospadias. These men have impaired fertility potential

due to variable development of the Wolffian Ducts as well as low volume and viscous ejaculations secondary to dihydrotestosterone deficiency [14].

While natural paternity in these patients is extremely rare, even after bilateral orchiopexy and male genital reconstruction, there are reports in the literature of successful pregnancies and live births using intrauterine insemination and IVF with ICSI [15,16]. TESE in case of azoospermia, could make paternity even more possible in men most severely affected by 5a-reductase type 2 deficiency.

Disorder of androgen action

Androgen insensitivity syndrome (AIS) is caused by mutations in the *androgen receptor (AR)* gene, and results in a partial or complete resistance to androgens [17].

Partial androgen insensitivity (PAIS) results in a more varied phenotype than the complete form of AIS (CAIS) depending on the residual androgen receptor function. The testes may be descended or not and the development of the Wolffian ducts may be normal or defective [18]. The spermatogenesis has been reported to range from azoospermia to complete spermatogenesis [19].

Men with PAIS have undervirilized external genitalia, including micropenis, hypospadias, and cryptorchidism. They present with oligo or azoospermia. Previous studies have reported cases with successful fertility in men with PAIS using assisted conception techniques and even a young men case having an *AR* mutation with a naturally offspring. This indicates that spontaneous fertility is possible in young men with confirmed PAIS [20].

PMDS

Mullerian Derivatives Persistence Syndrome (PMDS) is related to a defect in the anti-Mullerian hormone (AMH) or AMH receptor is characterized by the presence of Mullerian duct structures, including a cervix, uterus, fallopian tubes and upper two levels of vagina in an otherwise normally virilized boy with a 46,XY karyotype. Possible presentations are bilateral cryptorchidism, unilateral cryptorchidism with contralateral hernia or transverse testicular ectopia [21]. Abnormalities of the male excretory ducts are frequent. The testicles are normally differentiated and may present, if the cryptorchidism is not too old, germ cells.

Patients with PMDS have an increased risk of malignancy on the testes but also on the Müllerian structures [22]. Sexual function is normal but fertility is compromised. It is possible if at least one testicle is scrotal and its excretory ducts are intact [21]. Infertility is often due to aplasia of the epididymis and the upper part of the vas deferens which leads to poor connection of the testis with their excretory ducts.

Hypospadias

Hypospadias results from a defect in the development and closure of the urethral plate in the male, granting a urethral meatus on the ventral surface of the penis. When it is associated with cryptorchidism and/or micropenis, it is necessary to make an assessment to eliminate DSD. In the majority of cases of hypospadias, the urethral meatus is located over the glans, coronal sulcus, or distal shaft of the penis, but the meatal openings can also be more proximal.

Few studies have looked at fertility outcomes in men with hypospadias. Patients with distal hypospadias may have normal spermatogenesis, but data are limited. Men with proximal hypospadias have significantly decreased semen volume, sperm count, concentration, motility and sperm morphology [23]. In a large cohort of 350,835 men, including 2,484 with a diagnosis of hypospadias, hypospadias was associated with a 21% reduction in fatherhood [24]. A recent Swedish study showed that men born with hypospadias have lower overall offspring rates, an accumulated risk of being diagnosed with male infertility, and increased use of assisted reproductive technology (ART) [25].

Physical changes and/or the consequences of surgical correction, such as the development of a stricture, can also impact sexual and ejaculatory function and thus compromise fertility [26].

Undescended testes

Testicular descent occurs in two phases: a first phase of transabdominal descent at the 10th week of gestation and a second phase of inguinoscrotal descent at the 25th week of gestation [27,28]. This second phase involves an evagination of the peritoneum through the inguinal canal into the scrotum under the control of androgens [27,28]. Given this complex process, cryptorchid testes can be found at any point along the descent pathway or can also be found in other ectopic locations.

Infertility secondary to cryptorchidism is multifactorial and results mainly from a defect in spermatogenesis. Sperm abnormalities accompanied in 30% of men with unilateral cryptorchidism and in 80% of men with bilateral cryptorchidism [29]. International guidelines recommend orchidopexy before 18 months of age to avoid potential loss of fertility in adulthood [30]. In a large cohort of 350,835 men of whom 7,499 had a diagnosis of non-descending testes, having a history of non-descending testes was associated with a 21% reduction in paternity and a two-fold increase in use of ART [24]. For every 6-month delay in orchidopexy, there was a 5% increased risk of future ART use and a 1% reduction in fatherhood [24].

Understanding the needs of the patient

All of these data underline the need to improve and individualize care with a particular focus on the potential for fertility and the possibilities of becoming a parent. The indication for prophylactic gonadectomy, which was often performed in people with known DSD from early childhood, should be dispensed individually, depending on the potential risk of malignancy in the dysplastic gonad.

The types of fertility treatment that can be offered to patients with DSD are complex and close collaboration within multidisciplinary teams familiar with the problem is essential. Information about fertility and possible treatments given to patients with DSD should be given in an age-adapted manner, multiple times from childhood through adolescence and into adulthood until the patient is informed [31].

Psychological aspects, including sexuality, sexual orientation and psychosocial reasons, can also affect the possibility of having one's own children.

Adoption and surrogacy are suitable options for many people, but the procedures can be complicated by rules regarding economic as well as martial or civil partnership status and other preconditions set out by the country of origin of the child, with a cost that is not negligible for parents.

Moreover, the desire to have children is not a priority for everyone and the importance of having one's own children may vary considerably from one person to another.

Use of registries for studying fertility outcome

Registries can be a very effective tool for gathering data on natural history, variations in patient care and long-term clinical outcomes. By focussing on real world data, the evidence they provide are more likely to apply to a real-world situation. Registries may exist at regional, national or international levels and awareness and participation in these registries can be variable [32]. Many countries rountinely collect information from care records, systems and organisations on specific areas of health and care and this information is used to inform policy and monitor and improve care. However, these datasets have limited utility for conditions that are rare. Thus, rare disease registries that collect information on a particular condition or groups of conditions may prove beneficial. In the field of DSD, the I-DSD Registry, preceded by the EuroDSD Registry, has now been active for over a decade [33]. This registry and its associated network, play an increasingly important role in supporting research, training and benchmarking of care and service across the globe. In 2021, the network reached 260 centres in 63 countries on all 5 continents and of these, 115 centres from 40 countries had entered over 5,500 cases of all ages and with a median age of 17 years. A total of 54% of these individuals are male and the most commonly registered diagnoses are congenital adrenal hyperplasia (n, 1507, 28.4%), disorders of gonadal development (n, 1419, 26.7%) and disorders of androgen action (n, 674, 12.7%). The Registry has supported a wide range of studies in the field of DSD [34] but to date has not been used for studying fertility related outcomes.

Future direction

With the development of modern medical technologies, the question of managing the fertility of DSD patients opens the way to new perspectives. ART has developed rapidly over the past decades. Novel techniques, such as ICSI and testicular sperm retrieval, allow these patients to become biological parents. Some authors determine the presence of germ cells in the gonads of patients with DSD suggesting that the potential for fertility may be higher than previously thought [35].

ART has an increasing success rate and has become increasingly accessible. However, its availaibility varies greatly from one country to another, depending on the economic situation and the education of the individuals, but also on the ethical questions and the legislation of the different countries. Countries like Sweden, the Netherlands, the UK and France, that have full treatment coverage through national health plan and display the highest level of

ART use. Further international collaboration is recommended to examine the long-term fertility and access to parenthood outcomes of these patients, in order to continue to optimize their care.

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