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Review

Fertility in Disorders of Sex Development: Evidence and Uncertainties

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Objective and Rationale: This review examines the current evidence in fertility potential and treatment options for these rare disorders and highlights the areas of uncertainty to elucidate the importance and need for targeted research in this area of medicine.

Search methods: This review benefits from a PubMed literature review on fertility potential and treatment options available for DSD. The review is meant to be comprehensive, but not exhaustive of the relevant literature.

Wider implications: The intended audiences for this review are health care professionals who provide care to pediatric patients with DSD, including family medicine, primary care specialists, behavioral/mental health (psychology, social work and psychiatry), geneticists and genetic counselors, obstetricians/gynecologist, pediatric urologists and nurses. Nonetheless, we expect health professional students, educators, parents of children with DSD and adults with DSD will also read and benefit from this review.

Keywords: Assisted Reproductive Technologies (ART); Disorders of Sex Development (DSD); Fertility; Infertility; Intra-Cytoplasmic Sperm Injection (ICSI); *In-Vitro* Fertilization (IVF); Preimplantation Genetic Diagnosis (PGD); Testicular Sperm Extraction (TESE)

Abstract

Background: Recent developments in the field of medicine, genetics and biotechnology have led to a rethinking of optimal management in Disorders of Sex Development (DSD). In parallel, advancement in Assisted Reproductive Technologies (ART) has dramatically changed the fertility expectation of DSD patients and their families. Even though our knowledge remains incomplete, our understanding of fertility potential has improved significantly. Consequently, care providers are in a stronger position to advice patients affected by DSD (and their surrogates) in the decision-making process around fertility. Therefore, sharing of this knowledge with parents of the affected child and ongoing counseling by an infertility specialist should be considered an essential part of the interdisciplinary team approach.

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Introduction

Quality of life encompasses attraction, ability to develop intimate relationships, sexual functioning and the opportunity to rear children, regardless of biological indicators of sex [1]. Common problems encountered by persons with Disorders of Sex Development (DSD) include sexual inhibition elicited by anticipatory anxiety and lack of knowledge about fertility potential and treatments. Contributing to these problems are the understandable (and yet, counter-productive) reactions of parents to keep the child's condition secret, to protect them from being a subject of rumor and discrimination [2]. DSD are accompanied by substantial uncertainty regarding many aspects of the child's somatic development, including fertility potential. Communication and integration of this knowledge in shared decision making with parents and proper ongoing counseling by Reproductive Endocrinology and Infertility (REI) experts, are essential and should be a part of the interdisciplinary team approach.

The purpose of this review is to assist health care professionals in delivering sexual-wellbeing education, fertility potential and available treatment options, initially to the parents and, subsequently, to the patient following a staged and developmentally-sensitive schedule. This review reflects a comprehensive, but necessarily selective, literature review on fertility potential and treatment options for individuals with DSD, designed to address the substantial evidentiary gaps in the medical literature on DSD treatment.

Search Methods

We searched PubMed and MEDLINE from Jun. 1976 to Nov. 2016 for articles in English. Search words/terms were as follows: disorders of sex development, fertility, infertility, assisted reproductive technologies, *In-Vitro* fertilization, intra-cytoplasmic sperm injection, preimplantation genetic diagnosis, testicular sperm extraction,

ambiguous genitalia; gonadal dysgenesis, hypospadias, Müllerian remnants, ovotestis, Klinefelter syndrome, Turner syndrome, chimerism, androgen, congenital adrenal hyperplasia, AMH, LH, aromatase, cloacal exstrophy and Müllerian agenesis.

Disorders of Sex Development Classification

Sex chromosome DSD

Turner syndrome

Turner Syndrome (TS) is the most common cause of hypergonadotropic hypogonadism and primary ovarian insufficiency. It is characterized by a complete or partial absence or structural alterations of one of the X or Y-chromosomes [3]. TS presents with a range of clinical features; including varying degrees of gonadal dysgenesis due to accelerated loss of primordial follicles. The precise mechanism of follicular loss in TS is unknown. It has been postulated that gonadal dysgenesis may be a consequence of failure in sex chromosome pairing during meiotic prophase, resulting in a disruption of synaptic formation at the zygotene stage and subsequently causing oocyte loss. The degree of gonadal dysgenesis depends on the size of the unpaired region; severe pairing failure causes degeneration of nearly all of the oocytes due to activation of an apoptotic mechanism [4,5]. More than half of those with fewer TS features exhibit gonadal mosaicism (e.g., 45,X/46,XX) [6] with varying degrees of functional ovarian tissue resulting in some level of sexual development, menses and possible spontaneous pregnancy [7,8]. In the past, serum Anti-Müllerian Hormone (AMH) level has been shown to be a useful marker for the size of the growing follicle pool and primordial follicle pool, reflecting the ovarian reserve in adult cycling women and women at risk for Primary Ovarian Insufficiency (POI) [9,10]. Recent studies have shown that the level of serum AMH correlates with karyotype and ovarian function in TS and can be used as an excellent proxy measure of ovarian function and ongoing follicular development in prepubertal girls with TS to predict pubertal development and future fertility potential [11]. In the last three decades, fertility expectations have dramatically changed for women with TS. Through Assisted Reproductive Technologies (ART), more than 40% of the women with TS are able to achieve a pregnancy using their own or donor oocytes [12]. Most of the *In-Vitro* Fertilization (IVF) pregnancies resulting from using the patient's oocytes have been reported in women who experienced spontaneous puberty and continuous menstrual cycles.

Among women with TS and ovarian failure, IVF, using donated oocytes has resulted in a pregnancy rate similar to those using donated oocytes for other indications (56.6% success rate) [13]. Studies on obstetric and perinatal outcomes in TS oocyte donor pregnancies are few, but there is an exceptionally high risk of complications, including pregnancy-induced hypertensive disorders, preeclampsia, gestational diabetes, preterm labor, multiple gestation, low birth weight, sex chromosome abnormalities, spontaneous abortion or an inherent endometrial abnormality possibly associated with a deficiency of X-linked genes that regulate endometrial receptivity [14-16]. Additionally, the risk of death during pregnancy is increased as much as 100-fold, primarily due to complications of aortic dissection or rupture [17,18]. This risk is the greatest for those patients with pre-existing abnormalities such as a bicuspid aortic valve or a dilated aortic root, but all patients are subject to risk of death due to aortic dissection [19]. Consequently, TS should be regarded as a relative contraindication to pregnancy. Those who express serious interest in oocyte donation must receive thorough evaluation and counseling, and those having any significant cardiac abnormality should be strongly discouraged or offered surrogacy or gestational carrier cycles [17]. Preconception counseling should include screening for associated medical conditions, particularly the cardiovascular system by cardiology consultation. Thyroid status, renal function test, fasting blood glucose and oral glucose tolerance test should be assessed. The American Society for Reproductive Medicine (ASRM) practice committee recommends that any significant echocardiographic abnormality be considered an absolute contraindication of pregnancy in patients with TS [17]. The National Institute of Child Health and Human Development Guidelines further define this group as those with a history of bicuspid aortic valve, aortic dilation, or aortic coarctation [20]. An additional risk factor for cardiac complications includes the presence of multiple gestations. Therefore, in an IVF setting, with or without oocyte donation, a single embryo transfer should be considered, although monozygotic twinning may still occur (0.9-1.64% compared to 0.4% in general population). The possibility of selective reduction should be discussed [21]. The patient should be followed during the pregnancy by an interdisciplinary team of specialists, including the maternal fetal medicine expert, a cardiologist and an endocrinologist.

For some, oocyte donation may not be acceptable for personal, religious or legal reasons. In such cases, fertility preservation has been considered for selected women with TS. This approach is only applicable in patients with a mosaic karyotype, presence of ovarian follicles and a slower rate of germ cell loss [22,23]. Fertility preservation in adolescent girls with TS has recently been reported, but there is limited experience in using the preserved cells. The pregnancy success rate is unknown and the procedure is considered experimental.

Klinefelter syndrome

Klinefelter Syndrome (KS) is the most common cause of hypergonadotropic hypogonadism in males [24]. Men with KS may present with a variety of subtle, age-related and clinical signs. The gonads are almost always small and sperm production is usually severely decreased due to germ cell degeneration that commences *in utero* and progresses in adolescence. Histologically, gonads in KS contain extensive fibrosis with hyalinization of the seminiferous tubules and hyperplasia of the interstitium [25]. The underlying mechanism of the depletion of the germ cells in KS is unclear, however it is believed that insufficient supernumerary X-chromosome inactivation, Leydig cell insufficiency and disturbed regulation of apoptosis of Sertoli and Leydig cells are contributing factors [26,27]. Hypogonadism and infertility (azoospermia) becomes noticeable, at least by serum hormone determinations, from mid-puberty [25,28]. Cryptorchidism is by far the most common finding in boys and men with KS and this can further contribute to progressive and severe testicular damage [29]. If fertility is not desired, hypogonadism can be effectively managed with testosterone. However, if fertility is desired, testosterone supplementation should be postponed due to its negative effect on spermatogenesis. In this situation, fertility is possible through ART with Intra-cytoplasmic Sperm Injection (ART/ ICSI). In a substantial proportion of men with azoospermia, sperm can be obtained by Testicular Sperm Extraction (TESE) [30,31]. The crucial concern in KS patients is the potential transmission of genetic abnormalities to offspring by the retrieved spermatozoa. Some studies have demonstrated the higher prevalence of chromosomal aneuploidy, sex chromosomes and chromosomes 18 and 21, in sperms obtained from men with KS [32]. However, others have shown in non-mosaic KS males focal

spermatogenesis originates from euploid germ cells and therefore resulting in chromosomally normal gametes [33]. At present, majority of children born by ICSI in non-mosaic KS patients are chromosomally normal but most of them never had a genetic screening and thus the real genetic risk cannot be evaluated [34]. Given the conflicting observation most investigators recommend genetic counseling and standard prenatal diagnosis techniques. However, it remains an open question whether PGD should be offered to couples with KS male partner [35].

To date, more than 100 healthy children have been born after ICSI with testicular sperm from non-mosaic KS men. An initial success rate of 40-50% by TESE has been reported in a small series in adult males with 47,XXY [36]. A new technique, microdissection TESE (or Micro TESE), has shown significantly better sperm recovery rates (70%) compared to conventional TESE. Therefore, this technique should be favored over traditional TESE [34]. The only predictive factor for successful sperm recovery in KS seems to be testicular histopathology, but even without sperm in histological sections, TESE has proven successful. Live birth rates of 20-46% have been reported once sperm are obtained [31]. Neither testicular ultrasonography, extensive chromosome analysis, degree of virilization, testicular volume, nor serum testosterone, FSH, LH, or inhibin B levels are predictive of TESE outcomes. Even patients with unmeasurable inhibin B levels have undergone successful TESE [37]. In boys with KS, the markedly reduced number of adult spermatogonia indicates severely impaired fertility potential, even before puberty [25]. Cryopreservation of semen samples from KS boys in early puberty is a possible option and should be offered to appropriate patients before the start of testosterone supplementation [38]. The expected success rate is exceedingly low, since the onset of puberty initiates a marked acceleration in germ cell depletion and one must also take into account the limited ability of boys to provide semen samples during early puberty.

Other options for sperm cryopreservation in young boys who are unable to ejaculate are penile vibro-stimulation or rectal electro-stimulation under general anesthesia or TESE [39]. Studies have shown a successful sperm retrieval with TESE in KS boys despite a presence of decreased AMH and inhibin B and increased FSH [38,40,41]. However, the testis may contain spermatogonia and non-completely differentiated germ cells-spermatocytes and elongated spermatids. Nevertheless, these cryopreserved testicular samples containing immature spermatogonia would require *in vitro* maturation of spermatogonia into mature spermatozoa, or at least into late/elongated spermatids. Recent studies indicate that human testicular tissue can be cultured for at least 3 weeks without essential loss of spermatogonia, yielding normal spermatids with some fertilization potential [42,43]. However, at present this option for fertility preservation in pre-pubertal boys remains entirely experimental. It is important to counsel these patients and their parents about the fertility preservation options and procedures over a period of time beginning after the onset of puberty, when it is feasible to collect a semen sample, or when the patient is mature enough to consider alternative options and to accept the failure of germ cell retrieval [38,44].

47,XYY syndrome

The 47,XYY sex chromosome variant is the most common sex chromosome anomaly after KS (47,XXY). Men with an extra Y chromosome are mostly fertile. However, semen parameters are variable ranging from normal to azoospermia [45]. Multiple studies demonstrate that XYY men have a significant percentage of sperm mosaicism with varying degrees of arrested sperm maturation [46-48]. In contrast to XXY, cells with an XYY sex chromosome constitution can persist through meiosis due to premeiotic loss of an extra Y chromosome resulting in more euploid than aneuploid sperm cells [47]. Therefore, the level of germ cell mosaicism and meiotic sex chromosome configurations may determine sperm aneuploidy rate and fertility status in 47,XYY men.

Men with 47,XYY syndrome and normal sperm counts can potentially impregnate their partners. For those appearing to be infertile due to the high prevalence of oligospermia and abnormal sperm chromosomal constitution, IVF - with or without ICSI - may be an option [47]. These patients and their partners should receive genetic counseling to understand the potential risks to their offspring and be offered Preimplantation Genetic Diagnosis (PGD) [49]. Affected men with symptoms of hypogonadism or low total testosterone levels may benefit from empiric medical therapy such as clomiphene citrate or anastrozole to alleviate symptoms of hypogonadism and maximize intratesticular testosterone and spermatogenesis. There is no universal pattern for evaluation or identifying the ideal patient for such therapy [50]. Because there is no consensus on the optimal medication, along with considerable uncertainty on the efficacy of these therapies, this treatment is considered investigational.

45,X/46,XY

A mosaic 45,X/46,XY is the most frequent karyotype in patients with Mixed Gonadal Dysgenesis (MGD). 45,X/46,XY probably arises through anaphase lag during mitosis in the zygote. Clinically it is characterized by the existence of a dysgenetic testis on one side (thus associated with Wolffian derivatives and usually absence of Müllerian derivatives) and a streak gonad on the other side (therefore, no Wolffian remnants, hemi-uterus and Fallopian tube present) [51]. The genital phenotype ranges from a typical male with mild hypospadias or female phenotype to the presence of ambiguous genitalia with variable virilization of external genitalia. This variability reflects the relative proportions of 45,X and 46,XY cells in the gonadal ridge. In fact, this wide phenotypic spectrum is present in many DSD conditions [52].

Reports of fertility in these patients are limited. In a recent case series of 20 patients with MGD, none were fertile; 45% developed testicular failure necessitating testosterone replacement and 63% had Y chromosomal rearrangements with severely impaired fertility [53]. There are a few case reports on individuals with 45 X/46X(r) Y karyotype with oligozoospermia or oligoasthenoteratozoospermia who were able to conceive naturally or through ART/ ICSI [54,55]. Despite the fact that most patients with MGD are infertile, with very few reports of spermatogonia in semen and even fewer reports of successful conception, it is reasonable to consider TESE (or Micro TESE) and ICSI as a fertility option [56]. However, the risk of karyotypic abnormalities in the offspring necessitates genetic counseling or PGD.

Chimerism (46,XX/46,XY)

Chimeras, by definition, are mosaics. However, there is an important difference between chimeras derived from two zygotes and a single zygote that exhibits mosaicism due to an abnormality acquired during development [57]. Chimeras are a very rare occurrence

in humans, but the incidence is 10-20% in patients with ovotesticular DSD [58]. Recently, the use of amniocentesis has led to the incidental prenatal diagnosis of chimerism in individuals who have been found to have typical genitalia at birth. In these cases, the nature and function of the gonads are unknown [59,60]. Therefore, the true frequency of human chimerism detectable with current technology is unknown and the spectrum of associated clinical effects and fertility potential remain to be determined. To date, there is only one report available of a healthy pregnancy and delivery of 2 healthy babies to a woman with 46,XX/46,XY ovotesticular DSD following IVF/ICSI and Frozen Embryo Transfer (FET) [61]. In this case, the seminiferous tubule cells on histological examination by FISH were chimeric sex chromosome, 46,XX (18)/46,XY.

46,XY DSD

Complete gonadal dysgenesis (Swyer syndrome)

Swyer syndrome is an uncommon form of gonadal dysgenesis. Despite the presence of a single X and single Y chromosome, the phenotype is female because the dysgenetic (streak) gonads produce neither AMH nor androgens [62]. At least 10-15% of affected individuals carry a mutation of the SRY gene (Sex-determining Region of the Y chromosome) [63]. Mutations in NR5A1 and MAP3K1 genes also cause 46,XY complete gonadal dysgenesis [64,65]. In the remainder, no cause can be determined, although mutations in SRY regulatory elements or in other genes have been suggested [66,67]. Patients with Swyer syndrome exhibit normal growth, have no increased prevalence of any specific medical problems and therefore, do not require any specific monitoring or treatment beyond that relating to hormone replacement therapy aimed at inducing sexual maturation and fertility. Pregnancy by IVF using donor oocytes has not been associated with any specific risks or complications. The literature indicates a total of 15 pregnancies with successful delivery of healthy babies in women with Swyer syndrome. All pregnancies have been achieved through IVF donor cycles. The vast majority of the mothers underwent caesarian section; however, there are recent reports of a successful vaginal delivery [68,69]. There are some case reports on increased risk of pregnancy complications, such as hypertension or preeclampsia, but the true incidence and etiology of reported risks are unknown [70-72].

Testicular regression syndrome

Testicular regression syndrome (anorchia) is a condition in which normally developed testes during fetal life undergo prenatal regression or loss. The timing of loss and whether the loss is unilateral or bilateral, influence the degree of masculinization of internal and external genitalia in patients. Given the absence of testis or presence of nonfunctional fibrous and nodular testis, these patients are infertile. Fertility will be achieved by the use of donor sperm [73]. There is a report of testicular transplantation between 30 year-old twins for congenital anorchia in one twin with resumption of normal semen production by 90 days after the procedure [74]. It is not known whether this procedure would be successful in non-identical individuals.

Disorders in androgen synthesis

Disorders of androgen synthesis or action are rare, but they are recognized causes of 46,XY DSD.

17β-Hydroxysteroid dehydrogenase deficiencies: 17β-Hydroxysteroid Dehydrogenase Deficiency (HSD17B; also called 17-ketosteroid reductase deficiency) is a rare cause of 46,XY DSD [75]. It is inherited in an autosomal recessive pattern. Individuals with HSD17B present with testes and male Wolffian duct derived urogenital structures, but their external genitalia are undervirilized therefore they present as a female phenotype leading to a female gender announcement and gender of rearing. Puberty is associated with masculinization and 39-64% of cases reared as girls subsequently change their gender status due to extra testicular conversion of androstenedione to testosterone by unaffected HSD17B isoenzymes in peripheral tissues [76]. Early orchiectomy appears to be associated with stability of a female gender identity [77]. However, Phenotype may vary from mild forms with micropenis or hypospadias; undervirilization of external genitalia with or without clitoromegaly and/or labial fusion, to complete female external genitalia with testes situated in the abdomen, inguinal channels or in the labia major based on the enzyme activity [78].

Reports on fertility and sexual function in those affected by HSD17B are relatively limited. The histologic features of the testes may be normal in pediatric patients, but with age there is a progressive degeneration that includes atrophic Sertoli cells with basal membrane thickening, fibrosis and eventually, azoospermia [79]. A report of a patient with 17-ketosteroid reductase deficiency did not demonstrate the presence of spermatogenesis, despite early orchiopexy and normal serum testosterone [80]. Currently, there are no reports on fertility preservation or pregnancy in 17BHSD. It may be prudent to consider testicular biopsy and sperm cryopreservation in selected individuals followed by IVF/ICSI and PGD counseling. However, due to accelerated testicular fibrosis and evolving azoospermia, the application of this approach is entirely experimental and the expected success rate is low.

5α-Reductase type 2 deficiency: 5α-reductase type 2 deficiency is a 46,XY autosomal recessive disorder characterized by impaired virilization during embryogenesis secondary to impaired conversion of testosterone to Dihydrotestosterone (DHT). Fertility ranges from a complete lack of to normal spermatogenesis [81]. Currently, only 2 cases of spontaneous paternity have been documented in this syndrome [82]. A more severe enzyme defect precludes spontaneous parenthood and sperm recovery in the ejaculate (i.e., azoospermia). In these cases of unknown prevalence, the only fertility therapeutic possibility is TESE, which has been used as a successful strategy in a number of patients with non-obstructive azoospermia of various origins, including those with cryptorchidism [83]. TESE is also a reliable technique in providing information on the presence of spermatozoa in the testis for cryopreservation and future fertility preservation. Patients who desire imminent fertility may benefit from genetic counseling; the lack of a phenotype/genotype relationship makes it difficult, however, to reliably predict offspring phenotype.

Defects in androgen action

Complete Androgen Insensitivity Syndrome (CAIS) is a X-linked recessive disorder caused by inactivating mutations in the Androgen Receptor (AR) gene, whereas incomplete or Partial AIS (PAIS) describes a variety of disorders with less severe defects in androgen action [84]. The prevalence of PAIS in men with azoospermia or severe oligospermia is unknown, but it may be as high as 10% [85]. The spectrum of clinical presentations of PAIS can vary from a female phenotype with mild virilization to undervirilized males who may be fertile or infertile; testes are normally descended, but exhibit either

an absent germinal epithelium or spermatogenesis arrest [86]. Serum hormone levels in both severe and mild forms of PAIS are similar to CAIS [87]. Histologically, most seminiferous tubules show no spermatogenesis, but a small minority may exhibit complete spermatogenesis [88]. The fertility status of affected individuals depends on AR mutations that affect its function and emergent phenotype resulting from a dynamic interaction between the genome and proteome. There are four different types of AR mutations in AIS and according to each type, the phenotypic spectrum of may vary. Mutations that disrupt AR function result in the complete feminization of 46 XY individuals and the complete androgen insensitivity syndrome. Studies have revealed that AR mutations that do not lead to complete abrogation of its activity can cause a wide spectrum of milder androgen insensitivity syndromes, from ambiguous genitalia in newborn infants to `idiopathic' male infertility [89]. It has been shown the most common AR mutations in PAIS men with oligospermia are missense mutations in the steroid-binding domain that affects protein-protein interaction between receptor domain and co-activator proteins [90,91]. Additionally, studies have shown the relationship between the length of a trinucleotide repeat (CAG) tract, encoding a polyglutamine stretch in the transactivation domain of the AR and increased risk of defective spermatogenesis and undermasculinization [92]. Almost all men with PAIS are considered to be sterile and are advised to consider adoption or use of donor sperm.

There are limited case reports of paternity after pharmacological restoration of AR function with testosterone in men with minimal AIS, but it is rarely used and is usually unsuccessful [93]. There is a recent case report of successful pregnancy by TESE and ICSI in an azoospermic man with mild AIS [88]. Therefore, TESE may be an effective option followed by IVF/ICSI. The couple should receive genetic counseling and PGD is advised whenever possible [94]. The parents should be informed that their offspring will appear typical, but that daughters will carry the father's mutation and, subsequently, might transmit AIS to their sons [95]. Because of uncertainty about the genotype-phenotype correlation in mild forms of AIS, the phenotypic consequences of the mutation in offspring cannot be reliably predicted [96].

Luteinizing hormone receptor defects

Leydig cell hypoplasia is a rare autosomal recessive 46,XY DSD caused by inactivating mutations in the LH/CG receptor [97]. Patients with Leydig cell hypoplasia have varying degrees of spermatogenesis defects, ranging from azoospermia to normal spermatogenesis [98,99]. Fertility can be achieved by administration of Human Chorionic Gonadotropin (HCG) to increase testicular size, circulating level of testosterone and induction of spermatogenesis followed by ICSI [99]. Patients with Leydig cell hypoplasia should be offered genetic counseling and PGD only in cases with an identified mutation.

Disorders of AMH and AMH receptor (Persistent Müllerian Duct Syndrome)

Persistent Müllerian Duct Syndrome (PMDS) is a rare form of DSD characterized by the persistence of Müllerian duct derivatives in a male. The majority of PMDS cases are caused by mutations in the AMH or AMH receptor gene with the most common presentation being inguinal hernia, undescended testis or abdominal mass [100]. Approximately 200 cases of PMDS have been reported over the last 50 years; fertility potential is unknown [101]. Histologically, testes in PMDS are normal, but the epididymis does not appear completely typical and the uterus and the vasa open into the prostatic urethra close to each other. Males with PMDS may be fertile if Müllerian-derived structures have not compromised the integrity of the vasa deferens and orchidopexy was performed in a timely matter (typically less than one year of age) preventing significant germ cell hypoplasia. Therefore, it is possible that the reported infertility in PMDS has more to do with the structural abnormalities caused by the Müllerian remnants or it could be the result of long-term cryptorchidism or damage caused to the vas deferens during orchiopexy [101,102].

Fertility options in PMDS patients vary based on the cause of infertility. For example TESE is a viable option followed by IVF/ICSI in individuals with germ cell hypoplasia, whereas in obstructive cases due to structural abnormality or damage to vas deferens, the option could be Microsurgical Epididymal Sperm Aspiration (MESA), Percutaneous Epididymal Sperm Aspiration (PESA) or even TESE followed by IVF/ICSI. Microsurgical reanastomosis in cases with damage to vas is an alternative option; however one can postulate a low success rate or failure because the likelihood that sperm will return to the semen and pregnancy after microsurgical reanastmosis is inversely related to the duration of obstruction [103]. Since PMDS has an autosomal recessive inheritance pattern, genetic counseling before pregnancy is strongly encouraged.

46,XX DSD

46,XX DSD are predominantly a consequence of androgen excess, which may be of fetal, fetoplacental, or maternal origin.

Ovotesticular DSD

Ovotesticular DSD is a rare condition characterized by the development of mixed ovarian and testicular tissue, which may include bilateral ovotestes or an ovotestis with contralateral ovary or testis [58]. The majority of these patients have a 46,XX karyotype with chromosomal mosaicism and approximately 7% of patients have a 46,XY karyotype [104]. The genetics and pathophysiology of ovotesticular DSD are not well understood. There are 12 reported cases of spontaneous pregnancy in ovotesticular DSD patients and almost all had surgical removal of the testicular tissue before pregnancy. Surprisingly, all the fetuses have been male, and most pregnancies had the complications of preterm labor, neonatal death, or problems in delivery [105,106]. This suggests that removal of androgen-secreting testicular tissue may contribute to better ovulation in these women. Therefore, women with ovotesticular DSD and an intact female reproductive tract that are interested in fertility may benefit from excision of the testicular tissue to lower the androgens and possibly enhance the chances of ovulation [106]. The advantages of conservative surgery are not as marked in male patients since they are seldom fertile because of testicular dysgenesis and abnormalities of the vas deferens. Y chromosome genes are essential for spermatogenesis; hence, there is no possibility of finding sperm in the testis of men with ovotesticular or testicular DSD [107]. Therefore, the use of donor sperm is the only fertility option for the couple, but the male with ovotesticular DSD does not become fertile. Potential fertility and pregnancy in ovotesticular DSD may be underestimated and should be discussed when counseling these patients [108,109].

Testicular DSD

Testicular DSD is a rare syndrome in which the sex chromosomes (46,XX) are discordant with gonadal sex. Approximately 90% of the cases result from abnormal recombination and transfer of SRY from the Y to the X chromosome during male meiosis [110,111]. Other less likely causes include mutation in an autosomal or X chromosomal gene, which permits testicular determination in the absence of Testes Determining Factor (TDF) and undetected mosaicism with a Y-bearing cell line. It is now possible to identify two forms of this syndrome: Y DNA positive and Y DNA negative. The Y DNA positive males result from a X; Y translocation with a low recurrence risk; the Y DNA negative males are due to a mutation with a high recurrence risk [112].

After puberty these individuals present with normal pubic hair and penile size, but small testes and azoospermia [113]. Endocrine studies usually show hypergonadotropic hypogonadism secondary to testicular failure with elevated FSH, LH and decreased testosterone. Testicular biopsy typically reveals a decrease in the size and number of seminiferous tubules, peritubular fibrosis, absence of germ cells and hyperplasia of Leydig cells. Accordingly, these findings indicate permanent infertility in these individuals [114]. Donor sperm is the sole option for pregnancy in 46,XX men with testicular DSD.

Androgen excess

46,XX DSD are most commonly the consequence of excess exposure to androgens and their clinical manifestations depend on both the amount of DHT in the circulation and the timing of exposure.

Congenital adrenal hyperplasia

Classic congenital Adrenal Hyperplasia (CAH) is a genetic disorder caused by enzyme defects in adrenal cortisol biosynthesis. These conditions are inherited in autosomal recessive pattern. The most common cause of CAH is deficiency of the 21-Hydroxylase Enzyme (21-OHD) [115]; deficiencies of 11β-Hydroxylase (11-OHD) and 3β-Hydroxysteroid Dehydrogenase type 2 deficiencies (3β-HSD II) are less common [116]. Women with classical CAH have fewer pregnancies and children. This is attributable to chronic anovulation caused by excess production of adrenal androgens, progesterone or distorted pattern of gonadotropin secretion. Additional factors contributing to reduced fertility include: delayed psychosexual development, decreased sexual activity, reduced heterosexual activity and interest in parenting; abnormalities of genital anatomy, sexual dysfunction secondary to complications of early clitoroplasty and vaginoplasty; [117-119]. The fertility rate in women with 21-OHD correlates with the severity of the disorder and is significantly lower in woman with the salt wasting form than in those with the simple virilizing (less severe) form of CAH [120]. However, once pregnancy is achieved, outcomes among women with 21-OHD are normal except for an increased incidence of gestational diabetes and C-section due to stenosis or scarring of the vaginal canal after vaginoplasty and android pelvis characteristics increasing risk for cephalo-pelvic disproportion and dystocia [121]. Therefore, pregnant women with CAH should be monitored and delivered in a tertiary center with an experienced obstetrician to handle such pregnancies. Doses of glucocorticoids that do not cross the placenta, such as hydrocortisone and prednisolone should be adjusted to maintain maternal serum testosterone concentrations near the upper range of normal for pregnancy [122]. Children of mothers with 21-OHD have normal birth weight, intellectual and social development [120,123].

While 11-OHD is often considered the second most common cause of CAH, the disease is rare, occurring in only <1 in 100,000 births [124]. Like 21-OHD, women with 11-OHD experience irregular menses and hirsutism or male pattern baldness [125]. Hypertension is common, with a prevalence of 60-70% [126]; in cases of severe hypertension, cardiomyopathy, blindness and death have been reported [127]. Patients who desire pregnancy warrant management by a multidisciplinary team consisting of maternal fetal medicine and cardiology specialists. Women attempting pregnancy should stop Spironolactone and substitute intensified glucocorticoid therapy. A successful pregnancy has been reported in one woman with 11-OHD treated with Dexamethasone, Metformin and Clomid [128]. 3β-HSD II is an enzyme defect that impairs steroidogenesis in the adrenals and gonads, leading to glucocorticoid and mineralocorticoid deficiency [129]. Unlike 21-OHD, no data are available concerning pregnancy in women with 3β-HSD II [127]. PGD has greatly improved genetic counseling of families with CAH. In couples that are at risk for conceiving an affected child, PGD is able to detect affected embryos resulting from *In-Vitro* Fertilization (IVF). However, the ability of PGD to select the unaffected embryo for transfer is based on prior identification of the disease causing mutations in the family due to broad range of mutations causing CAH [130].

Feto-Placenta enzyme deficiency

Aromatase deficiency and P450 oxidoreductase deficiency are the two rare enzyme deficiencies associated with androgen excess. They are distinct from classical CAH because both involve the fetal adrenal and the placenta. Aromatase deficiency is a rare autosomal recessive disorder in which fetal androgens are not converted to estrogens. This can cause virilization of female fetuses and maternal hirsutism. At puberty, affected females experience hirsutism, acne and primary amenorrhea with hypergonadotropic hypogonadism and multiple enlarged ovarian cysts (4-8cm) [131]. The few studies of males with aromatase deficiency reported normal pubertal development, but semen analysis revealed oligospermia with or without asthenospermia. A causal relationship between sperm problems and aromatase deficiency is uncertain [132]. Animal models of male aromatase deficiency indicate that local expression of aromatase is essential for germ cell development and spermatogenesis, but data in humans are lacking [133]. Currently, there is a lack of information about the course of the disease in adulthood and long-term consequences for fertility in aromatase-deficient patients. P450 Oxidoreductase (POR) enzyme deficiency is perhaps the most complex form of CAH because it affects the activity of all of the P450 enzymes involved in steroidogenesis. POR, in contrast to Polycystic Ovarian Syndrome (PCOS), is associated with hypoandrogenemia secondary to lack of steroid production and hypergonadotropic hypogonadism [134,135]. Skeletal abnormalities in POR are diagnosed as Antley-Bixler syndrome (craniosynostosis, choanal atresia, radial humeral synostosis) [136]. The milder form of POR has been reported with both male and female infertility without associated skeletal anomalies [137,138]. The long-term outcome in POR deficiency is incompletely understood and, to date, no pregnancy has been reported. Because multiple enzymes that affect reproductive organ function are defective, one may speculate that pregnancy could be achieved through donor cycles and surrogacy due to the additional destructive effect of the disease on the endometrium.

Non-Hormonal DSD

Müllerian agenesis

Müllerian agenesis is a relatively common cause of primary amenorrhea. It is characterized by absence of the vagina, an absent or hypoplastic uterus, and normal or hypoplastic fallopian tubes [139]. Since ovaries are not derived from Müllerian ducts, these patients are able to have genetic offspring through gestational surrogacy. Although pregnancy and delivery have been achieved in a number of cervicovaginal agenesis patients in whom McIndoe vaginoplasty was performed, to date no pregnancy has been reported in cervicovaginal agenesis patients treated with intestinal vaginoplasty [140]. Recent advancement in uterine transplantation has provided a promising future for pregnancy in individuals with Müllerian agenesis [141].

Mayer-Rokitansky-Küster-Hauser syndrome (MRKH)

MRKH is a disorder characterized by utero-vaginal atresia in a female with a typical external genital phenotype, 46,XX karyotype and normal functioning ovaries [142]. Affected women usually present with primary amenorrhea. MRKH may be isolated (type I), but it is more frequently associated with renal, vertebral, and, to a lesser extent, auditory and cardiac defects (MRKH type II or MURCS association) [143]. For a long time the syndrome has been considered a sporadic anomaly, but increasing number of familial cases now support the hypothesis of a heritable cause [144]. In familial cases, the syndrome appears to be transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity. However, the etiology of MRKH syndrome remains unclear.

Fertility in women with MRKH has been achieved by IVF/surrogacy [145]. A large retrospective study conducted in 1997, consisting of 162 IVF/surrogacy pregnancies, did not show any increased risk of congenital anomaly in offspring; however, due to the survey nature of the study, the associated congenital abnormality in MRKH patients is not clear [146]. Risk of transmission to offspring is unknown due to limited data. Introducing a uterine transplant was a breakthrough in the field of reproductive medicine for treatment of uterine factor infertility (e.g., MRKH). As of today, a total of eleven cases of human uterus transplantations have been reported worldwide, conducted in three different countries [147-149]. The results of these initial experimental cases far exceed what might be expected. The first human live birth was reported in 2014 [150]. The recipient, a 35-year-old woman with MRKH syndrome, was transplanted with a live donor uterus from a 62-year-old postmenopausal family friend. Menstruation occurred 43 days post surgery and continued with regular intervals (26-36 days). Twelve months after the transplantation, the organ recipient had a single embryo-transfer that was immediately successful and resulted in a live birth of healthy boy at 31.5 week via C-section [150]. However, one should keep in mind that this procedure is still investigational and before introducing uterus transplantation in a wider general setting, several more carefully monitored pregnancies are required to evaluate major obstetrical risks, including miscarriage, preeclampsia, preterm birth, and fetal growth restriction.

Cloacal exstrophy

Cloacal exstrophy is a rare and complex malformation in which the rectum, vagina and urinary tract share a common orifice [151]. Cloacal extrophy is the most severe form of the bladder-exstrophy-epispadias-cloacal exstrophy complex [152]. The intermediate form of the disease is bladder exstrophy in which the bladder is open from the top of the bladder through the urethra and to the tip of the penis [153,154]. There are limited long-term data on genital function and potential fertility of adolescent and young adult patients with cloacal exstrophy. In males, the main problem is reported to be the delivery of sperm to the vagina even after corrective surgery [155]. Unfortunately, many men with exstrophy do not ejaculate or lack a forceful ejaculation because of the absence of a circular prostate and a bulbospongiosus muscle [156]. Despite difficulty in ejaculation, at least some kind of ejaculation has been reported in 75% of cases and about 50% of the male patients were able to father children after diversion or constructive surgery [157]. Because of the eccentricities of ejaculation, it makes it difficult to collect semen for analysis; however, the presence of even a few sperm in semen analysis indicate that spermatogenesis is occurring and fertility with some techniques of assisted reproduction or electro-ejaculation may be possible. In cases of inability or lack of semen, testicular biopsy and subsequently Percutaneous Epididymal Sperm Aspiration (PESA) or TESE may provide sperm for ICSI and fertilization. Absence of sperm in testicular biopsy is an indication for donor sperm [158-160]. In females, anomalies of the genitalia include absence or duplex clitoris and vagina and bicornuate uterus. The adnexa, including the ovary and fallopian tube, are usually normal, leading to the potential for normal fertility [157,161].

In an observational study of fertility and obstetric outcomes involving the largest cohort of female patients with classical bladder extrophy [162], 68% of those attempting conception were successful; 21% with spontaneous pregnancy within 1 year and 26% after having received fertility treatments. Overall, this report suggests that women with bladder exstrophy may experience difficulty with fertility, most likely the result of tubal obstruction or some other genital complication following surgical reconstruction. Currently, more than 80 pregnancies in women with bladder exstrophy have been reported [162]. Pregnancy is high risk for both mother and fetus with higher risk of urinary infection, pelvic prolapse, C-section, prematurity and stillbirth. A preconception renal evaluation for all women in this group should be offered in an effort to optimize renal function [162]. Additionally due to higher risk of prenatal morbidity, single embryo transfer is strongly recommended in patients who undergo IVF treatment. Although vaginal delivery has been described, it should be avoided as it may jeopardize previous reconstruction and subsequently lead to urinary incontinence. Therefore, elective caesarian section by experienced staff is strongly recommended before the onset of labor.

The literature has shown a 400-fold increased risk of cloacal exstrophy in offspring of affected individuals [163], but not of any other congenital anomalies. Accordingly, these patients need an interdisciplinary approach that includes an urologist, reproductive endocrinologist and experienced obstetrician.

Future Directions

In the last three decades, fertility expectations have clearly changed for patients with DSD. Reproductive endocrinology and infertility specialists should be considered a part of the interdisciplinary treatment team. Fertility issues should be discussed with patients (or their surrogates) from the beginning because decisions regarding gender assignment, genital and/or gonadal surgery may hinge upon this information. With recent advances in ART, the possibility of pregnancy and having children is becoming more realistic for patients who

previously have not had many fertility options. The current obstacle in fertility counseling of patients with DSD is a lack of or limited data on fertility potential and treatment options (Table 1); there is therefore a strong need for more research and investigation on fertility potential, management, treatment and outcome of treatment and ultimately fertility preservation.

Disorder of Sex Development	Fertility	Treatment
Sex Chromosome DSD		
Turner syndrome (45X; 45X/46XX)	Severe forms: Streak gonads with no oocyte Mosaic: Early diminished ovarian reserve or POI	**Severe forms:** Motherhood possible with oocyte donation (high-risk pregnancies) **Mosaic:** Pregnancy through ART or 2-7% spontaneous pregnancy [4,8] Possibility of oocyte cryopreservation (fertility preservation through ovarian tissue cryopreservation in pediatrics and adolescence is still investigational)
Klinefelter syndrome (47XXY)	Severe decreased sperm production with small testes	Fatherhood is possible by TESE or MicroTESE with IVF/ICSI. Fertility preservation through sperm cryopreservation in early puberty (fertility preservation through testicular tissue cryopreservation and *in vitro* maturation of immature sperm is investigational)`
47, XYY syndrome	Varying degree of infertility ranging from normal fertility to azoospermia. High prevalence of abnormal sperm chromosomal constitution	**Severe forms:** IVF with or without ICSI based on semen analysis **Milder forms:** Possible clomiphene citrate or anastrozole (no clear and universal consensus)
45,X/46,XY (MGD)	Variable phenotype from complete gonadal failure to oligozoospermia or oligoasthenoteratozoospermia	Fertility possible through TESE or Micro TESE with IVF/ICSI
46,XX/46,XY (Chimerism, Ovotesticular DSD)	Unknown nature or function of gonad with regards to fertility potential	Unknown
46, XY DSD		
Complete Gonadal Dysgenesis (Swyer syndrome)	Streak gonads	Motherhood possible with oocyte donation (high-risk pregnancy)
Testicular Regression syndrome	Streak testes or no testes	Fatherhood is possible by donor sperm (a case report on successful testicular transplant in identical twin)
Disorders in Androgen Synthesis 17- hydroxysteroid dehydrogenase deficiency 5α-reductase deficiency	Non functional testes and eventually gonadal failure and azoospermia Based on enzyme activity varies from normal spermatogenesis to azoospermia	No reports on fertility preservation or pregnancy 2 case reports of spontaneous pregnancy. In azoospermia: TESE or MicroTESE followed by IVF/ICSI and sperm cryopreservation for future fertility
Defects in Androgen Action Androgen insensitivity syndrome	Azoospermia and gonadal failure	**Mild forms**: TESE or MicroTESE followed by IVF/ICSI **Severe forms:** Donor sperm
Luteinizing Hormone Receptor Defects Leydig cell hypoplasia, aplasia	Varies ranging from azoospermia to normal spermatogenesis	Human chorionic gonadotropin (HCG) injection followed by IVF/ICSI
AMH/AMH Receptor Defects	Unknown	MESA, PESA, TESE followed by IVF/ICSI Microsurgical reanastmosis in cases with damage to vas but low success rate
46, XX DSD		
Ovotesticular DSD	Varies from functional gonad to gonadal failure	Case reports of spontaneous pregnancy after removal of testicular tissue gonad. No reports on fertility in male
Testicular DSD	Hypergonadotropic hypogonadism with azoospermia	Fatherhood is possible by donor sperm
Androgen Excess 21-hydroxylase deficiency; 11 - hydroxylase deficiency & 3-β hydroxysteroid II deficiency	Hyperandrogenemia and ovulatory dysfunction	1. Intensify glucocorticoid therapy 2. If glucocorticoid therapy fails to induce ovulation, consider ART 21-hydroxylase deficiency: high-risk pregnancy and increase miscarriage rate 11-hydroxylase deficiency: high risk pregnancy 3BHSD deficiency: No data on pregnancy
Feto-Placenta Enzyme Deficiency Aromatase Deficiency POR (P450 oxidoreductase)	Male: Oligospermia with or without asthenospermia Female: hypergonadotropic hypogonadism Hypergonadotropic hypogonadism with hypoandrogenemia	No data on fertility potential and options No report on pregnancy and no data on fertility potential and options
Non-hormonal DSD Müllerian Agenesis (MRKH) Cloacal exstrophy (Bladder-exstrophy-epispadias-cloacal exstrophy complex)	Normal gonads Male: Difficulty in ejaculation Female: Normal ovaries	Motherhood through gestational surrogacy (possible uterine transplantation, but still investigational) **Male:** 50% spontaneous fatherhood after reconstructive surgery Ejaculatory dysfunction: Electro-Ejaculation (EJ); if no sperm in ejaculate, PESA or TESE followed by IVF/ICSI; If no sperm in TESE: donor sperm **Female:** Spontaneous pregnancy has been reported with elective C-section (high-risk pregnancy)

Table 1: DSD: Summary of fertility potential and options.

POI: Primary Ovarian Insufficiency; ART: Assisted Reproductive Technologies; TESE: Testicular Sperm Extraction; IVF: *In-Vitro* Fertilization; ICSI: Intra-Cytoplasmic Sperm Microinjection; PESA: Percutaneous Epididymal Sperm Aspiration.

Author's Roles

Nastaran Foyouzi Contribution: 1) substantial contributions to conception and design, literature search and acquisition of data and interpretation of data, 2) drafting the article for important intellectual content and 3) final approval of the version to be published.

David Sandberg Contribution: 1) contributions to conception and design, literature search and acquisition of data 2) help in drafting the article for important intellectual content, and 3) final approval of the version to be published.

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