Fertility in Disorders of Sex Development: Evidence and Uncertainties

Nastaran Foyouzi1,2* and David E Sandberg3

1Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, University of Michigan, Ann Arbor, MI, 48104, Michigan, USA
2Department of Human Genetics, University of California in Los Angeles, Los Angeles, California, USA
3Department of Pediatrics and Communicable Diseases, Division of Pediatric Psychology and the Child Health Evaluation & Research (CHEAR) Unit, University of Michigan, Ann Arbor, Michigan, USA

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/gynecologists, 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)

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 extrophy 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 zygote 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,XXX [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 spermatooza, 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,XY syndrome

The 47,XY 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 XXY 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 oligosperma 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 hyponogadism or low total testosterone levels may benefit from empiric medical therapy such as clomiphene citrate or anastrozole to alleviate symptoms of hyponogadism 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 oligospermia 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 chromosomal, 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 orchitectomy 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 orchiohypoxia 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 spermatogenesis 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 vasa 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 vasa 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 vasa 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 reanastomosis is inversely related to the duration of obstruction [103]. Since PMDS has an autosome 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 somatosexual 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 hypergonadotropin hypergonadism 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 11ß-Hydroxylase (11-OHD) and 3ß-Hydroxysteroid Dehydrogenase type 2 deficiencies (3ß-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 psychosocial 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 women 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]. 3ß-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 3ß-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 MRUCS 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 pregnancy in individuals with Müllerian agenesis patients [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].

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 extrophy 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 extrophy 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 extrophy 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 form of the disease is bladder extrophy 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 extrophy. 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 extrophy 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 reconstructive 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].
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 |
|----------------------------|-----------|-----------|
| 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 pregnancy). Mosaic: Pregnancy through ART or 2-7% spontaneous pregnancy. 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 ovum maturation of immature sperm is investigational). |
| 47, XYV syndrome | Varying degree of infertility ranging from normal fertility to azoospermia. High prevalence of abnormal sperm chromosomal constitution | Severe forms: IFV 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 oligoospermia 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 |

### 40, 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 spermato genesis 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: Azoospermia and gonadal failure. Mild forms: TESE or MicroTESE followed by IVF/ICSI. Severe forms: Donor sperm.
- Lateonizing 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. 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 3BHS deficiency: No data on pregnancy.
- Feto-Placenta Enzyme Deficiency: Aromatase Deficiency PO/P (P450 oxidoreductase) Male: Oligospermia with or without asthenospermia Female: hypergonadotropic hypogonadism Hypergonadotropic hypogonadism with hypopandrogenemia. No data on fertility potential and options. No report on pregnancy and no data on fertility potential and options.
- Non-functional 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-Vivo Fertilization; ICSE: 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.

Acknowledgement

Sally Camper- James V. Neel Professor and Chair of Department of Human Genetics, University of Michigan, Ann Arbor, MI, 48109.

Funding

This work was supported, in part, by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01 HD068138; the DSD - Translational Research Network).

Disclosures

Authors report no conflict of interest.

References

1. Lee PA, Houk CP, Ahmed SF, Hughes IA (2006) Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics 118: 488-500.

2. Sandburg DE, Mazur T (2014) A noncategorical approach to the psychosocial care of persons with DSD and their families. In: Baudewijnje PC, Kreukels, Thomas D, Steensma, Annelou LC, et al. (eds.). Gender Dysphoria and Disorders of Sex Development. Focus on Sexuality Research. Pg no: 93-114.

3. Bondy CA (2009) Turner syndrome 2008. Horm Res 71: 52-56.

4. Abir R, Fisch B, Nahum R, Orvieto R, Nitke S, et al. (2001) Turner’s syndrome and fertility: Current status and possible putative prospects. Hum Reprod Update 7: 603-610.

5. Ogata T, Muroya K, Matsuo N, Shinohara O, Yorifuji T, et al. (2001) Turner syndrome and Xp deletions: Clinical and molecular studies in 47 patients. J Clin Endocrinol Metab 86: 5498-5508.

6. Turner C, Dennis NR, Skuse DH, Jacobs PA (2000) Seven ring (X) chromosomes lacking the XIST locus, six with an unexpectedly mild phenotype. Hum Genet 106: 93-100.

7. Gravholt CH, Fedder J, Naeraa RW, Muller J (2000) Occurrence of gonadoblastoma in females with Turner syndrome and Y chromosome material: a population study. J Clin Endocrinol Metab 85: 3199-3202.

8. Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, et al. (2001) Recommendations for the diagnosis and management of Turner syndrome. J Clin Endocrinol Metab 86: 3061-3069.

9. van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancs LF, et al. (2002) Serum anti-Mullerian hormone levels: A novel measure of ovarian reserve. Hum Reprod 17: 3065-3071.

10. Visser JA, de Jong FH, Laven JS, Themmen AP (2006) Anti-Mullerian hormone: A new marker for ovarian function. Reproduction 131: 1-9.

11. Visser JA, Hekken-Koelega AC, Zandwijk GR, Limacher A, Ranke MB, et al. (2013) Anti-Mullerian hormone levels in girls and adolescents with Turner syndrome are related to karyotype, pubertal development and growth hormone treatment. Hum Reprod 28: 1899-1907.

12. Bodri D, Vernaeve V, Figueras F, Vidal R, Guillen JJ, et al. (2006) Oocyte donation in patients with Turner’s syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy. Hum Reprod 21: 829-832.

13. Fouladi T, Soderstrom-Antilla V, Hovatta O (1999) Turner’s syndrome and pregnancies after oocyte donation. Hum Reprod 14: 532-535.

14. Sheffer-Mimouni G, Mashiah S, Dor J, Levran D, Seidman DS (2002) Factors influencing the obstetric and perinatal outcome after oocyte donation. Hum Reprod 17: 2636-2640.

15. Stoop D, Baumgarten M, Haentjens P, Polyzos NP, De Vos M, et al. (2012) Obstetric outcome in donor oocyte pregnancies: A matched-pair analysis. Reprod Biol Endocrinol 10: 42.

16. Yaron Y, Ochshorn Y, Amit A, Yovel I, Kogosowski A, et al. (1996) Patients with Turner’s syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation. Fertil Steril 65: 1249-1252.

17. Practice Committee of American Society for Reproductive Medicine (2012) Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. Fertil Steril 97: 282-284.

18. Matura LA, Ho VB, Rosing DR, Bondy CA (2007) Aortic dilatation and dissection in Turner syndrome. Circulation 116: 1663-1670.

19. Landin-Wilhelmsen K, Bryman I, Wilhelmsen L (2001) Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. J Clin Endocrinol Metab 86: 4166-4170.

20. Bondy CA (2008) Congenital cardiovascular disease in Turner syndrome. Congenit Heart Dis 3: 2-15.

21. Chang HJ, Lee JR, Lee BC, Suh CS, Kim SH (2009) Impact of blastocyst transfer on offspring sex ratio and the monoygotic twinning rate: A systematic review and meta-analysis. Fertil Steril 91: 2381-2390.

22. Lau NM, Huang JY, MacDonald S, Elizur S, Gidoni Y, et al. (2009) Feasibility of fertility preservation in young females with Turner syndrome. Reprod Biomed Online 18: 290-295.

23. El-Shawarby SA, Sharif F, Conway G, Serhal P, Davies M (2010) Oocyte cryopreservation after controlled ovarian hyperstimulation in mosaic Turner syndrome: another fertility preservation option in a dedicated UK clinic. BJOG 117: 234-237.

24. Bojesen A, Juul S, Gravholt CH (2003) Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 88: 622-626.

25. Wikström AM, Raivio T, Hadziselimovic F, Wikström S, Tuuri T, et al. (2004) Klinefelter syndrome in adolescence: onset of puberty is associated with accelerated germ cell depletion. J Clin Endocrinol Metab 89: 2263-2270.

26. Aksgaård L, Wikstrom AM, Raipjert-De Meyts E, Dunkel L, Skakkebaek NE, et al. (2006) Natural history of seminiferous tubule degeneration in Klinefelter syndrome. Hum Reprod Update 12: 39-48.

27. Paduch DA, Bolyakov A, Cohen P, Travis A (2009) Reproduction in men with Klinefelter syndrome: the past, the present, and the future. Semin Reprod Med 27: 137-148.

28. Bastida MG, Rey RA, Bergada I, Bedecarras P, Andreone L, et al. (2007) Establishment of testicular endocrine function impairment during childhood and puberty in boys with Klinefelter syndrome. Clin Endocrinol (Oxf) 67: 863-870.

29. Schwartz ID, Root AW (1991) The Klinefelter syndrome of testicular dysgenesis. Endocrinol Metab Clin North Am 20: 153-163.

30. Wikström AM, Dunkel L (2011) Klinefelter syndrome. Best Pract Res Clin Endocrinol Metab 25: 239-250.
31. Schif JD, Palermo GD, Veeck LL, Goldstein M, Rosenwaks Z, et al. (2005) Success of testicular sperm extraction [corrected] and intracytoplasmic sperm injection in men with Klinderfeld syndrome. J Clin Endocrinol Metab 90: 6263-6267.

32. Staessen C, Tournoy H, Van Asche E, Michiels A, Van Landuyt L, et al. (2003) PGD in 47,XXY Klinderfeld’s syndrome patients. Hum Reprod Update 9: 319-330.

33. Scirrano RB, Luna Hisano CV, Rahn MJ, Brugo Olmedo S, Rey Valzacchi G, et al. (2009) Focal spermatogenesis originates in euploid germ cells in classical Klinderfeld patients. Hum Reprod 24: 2353-2360.

34. Fullerton G, Hamilton M, Maheshwari A (2010) Should non-mosaic Klinderfeld syndrome men be labelled as infertile in 2009? Hum Reprod 25: 588-597.

35. Greco E, Scarcelli F, Minagi MG, Casciani V, Zavaglia D, et al. (2013) Birth of 16 healthy children after ICSI in cases of nonmosaic Klinderfeld syndrome. Hum Reprod 28: 1155-1160.

36. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E (2004) Klinderfelder’s syndrome. Lancet 364: 273-283.

37. Vernaeve V, Staessen C, Verheyen G, Van Steirteghem A, Devroey P, et al. (2013) Klinefelter syndrome men be labelled as infertile in 2009? Hum Reprod 28: 1155-1160.

38. Rives N, Milazzo JP, Perdrix A, Castanet M, Joly-Hélas G, et al. (2013) Impaired puberty, fertility, and final stature in 45,46,XY mixed gonadal dysgenetic patients raised as boys. Eur J Endocrinol 166: 687-694.

39. Damani MN, Mittal R, Oates RD (2001) Testicular tissue extraction in a young male with 47,XXY Klinefelter’s syndrome: potential strategy for preservation of fertility. Fertil Steril 76: 1054-1056.

40. Kalsi JS, Shah P, Thum Y, Muneer A, Ralph DJ, et al. (2015) Salvage micro-dissection testicular sperm extraction: outcome in men with non-obstructive azoospermia with previous failed sperm retrievals. BJU Int 116: 460-465.

41. Ferhi K, Avakian R, Griveau JF, Guille F (2009) Age as only predictive factor for successful sperm recovery in patients with Klinderfeld’s syndrome. Andrologia 41: 84-87.

42. Larsen HP, Thornj, Skovgaard LT, Cortes D, Byskov AG (2002) Long-term cultures of testicular biopsies from boys with cryptorchidism: effect of FSH and LH on the number of germ cells. Hum Reprod 17: 383-389.

43. Sousa M, Cremades N, Alves C, Silva J, Barros A (2002) Developmental potential of human spermatogenic cells co-cultured with Sertoli cells. Hum Reprod 17: 161-172.

44. Gies I, Tournoy H, De Schepper J (2016) Attitudes of parents of Klinefelter boys and pediatricians towards neonatal screening and fertility preservation techniques in Klinefelter syndrome. Eur J Pediatr 175: 399-404.

45. Abdel-Razic MM, Abdel-Hamid IA, ElSobky ES (2012) Nonmosaic 47,XXY syndrome presenting with male infertility: case series. Andrologia 44: 200-204.

46. El-Dahtory F, Elsheikha HM (2009) Male infertility related to an aberrant karyotype, 47,XY: four case reports. Cases J 2: 28.

47. Rives N, Milazzo JP, Miraux L, North MO, Sibert L, et al. (2005) From spermatocytes to spermatozoa in an infertile XYY male. Int J Androl 28: 304-310.

48. Wong EC, Ferguson KA, Chow V, Ma S (2008) Sperm aneuploidy and meiotic sex chromosome configurations in an infertile XY male. Hum Reprod 23: 374-378.

49. Gonzalez-Merino E, Hans C, Abramowicz M, Englert Y, Emiliani S (2007) Aneuploidy study in sperm and preimplantation embryos from nonmosaic 47,XXY men. Fertil Steril 88: 600-606.

50. Kim JW, Khadirar AC, Ko EY, Sabaneh ES Jr (2013) 47,XXY Syndrome and Male Infertility. Rev Urol 15: 188-196.

51. Achermann JC, Hughes IA (2011) Disorders of Sex Development.

52. El Moussaif N, Haddad NE, Iraqi N, Gauzi A (2011) 45,X/46,XY mosaicism: Report of five cases and clinical review. Ann Endocrinol (Paris) 72: 239-243.

53. Martinerie L, Morel Y, Gay CL, Pienkowski C, de Kerdanet M, et al. (2012) Impaired puberty, fertility, and final stature in 45,46,XY mixed gonadal dysgenetic patients raised as boys. Eur J Endocrinol 166: 687-694.

54. Bofinger MK, Needham DF, Saldana LR, Sosnowski JP, Blough RI (1999) 45,X/46,XY karyotype transmitted by father to son after intracytoplasmic sperm injection for oligospermia. A case report. J Reprod Med 44: 645-648.

55. Blanco J, Farreras A, Egozcue J, Vital F (2003) Meiotic behavior of the sex chromosomes in a 45,X,46,X.r(Y) karyotype transmitted by father to son after intracytoplasmic sperm injection for oligospermia. J Reprod Med 49: 913-918.

56. Flannigan RK, Chow V, Ma S, Yuzpe A (2014) 45,46,XY mixed gonadal dysgenesis: A case of successful sperm extraction. Can Urol Assoc J 8: 108-110.

57. Boklage CE (2006) Embryogenesis of chimeras, twins and anterior midline asymmetries. Hum Reprod 21: 579-591.

58. Krob G, Braun A, Kuhnle (1994) U True hermaphroditism: geographical distribution, clinical findings, chromosomes and gonadal histology. Eur J Pediatr 153: 2-10.

59. Malan V, Gesny R, Morichon-Delvallez N, Aubry MC, Benachi A, et al. (2007) Prenatal diagnosis and normal outcome of a 46,XX/46,XY chimera: a case report. Hum Reprod 22: 1037-1041.

60. Binkhorst M, de Leeuw N, Otten BJ (2009) A healthy, female chimera with 46,XX/46,XY karyotype. J Pediatr Endocrinol Metab 22: 97-102.

61. Sugawara N, Kimura Y, Araki Y (2012) Successful second delivery outcome using refrozen thawed testicular sperm from an infertile male true hermaphrodite with a 46,XX/46,XY karyotype: case report. Hum Cell 25: 96-99.

62. Berkovitz FD, Fechner PY, Zaucz H, Rock JA, Snyder HM 3rd, et al. (1991) Clinical and pathologic spectrum of 46,XY gonadal dysgenesis: its relevance to the understanding of sex differentiation. Medicine (Baltimore) 70: 375-383.

63. Sanchez-Moreno I, Canto P, Munguia P, de Leon MB, Cisneros B, et al. (2009) DNA binding activity studies and computational approach of mutant SRY in patients with XY/XX SRY chimera. J Pediatr endocrinol metab 29: 212-218.

64. Kohler B, Lin L, Ferraz-de-Souza B, Vieacker P, Heidemann P, et al. (2003) PGD in 47,XXY Klinefelter syndrome. Hum Reprod 18: 108-110.

65. Malan V, Gesny R, Morichon-Delvallez N, Aubry MC, Benachi A, et al. (2007) Prenatal diagnosis and normal outcome of a 46,XX/46,XY chimera: a case report. Hum Reprod 22: 1037-1041.

66. Binkhorst M, de Leeuw N, Otten BJ (2009) A healthy, female chimera with 46,XX/46,XY karyotype. J Pediatr Endocrinol Metab 22: 97-102.

67. Sugawara N, Kimura Y, Araki Y (2012) Successful second delivery outcome using refrozen thawed testicular sperm from an infertile male true hermaphrodite with a 46,XX/46,XY karyotype: case report. Hum Cell 25: 96-99.

68. Berkovitz FD, Fechner PY, Zaucz H, Rock JA, Snyder HM 3rd, et al. (1991) Clinical and pathologic spectrum of 46,XY gonadal dysgenesis: its relevance to the understanding of sex differentiation. Medicine (Baltimore) 70: 375-383.

69. Sanchez-Moreno I, Canto P, Munguia P, de Leon MB, Cisneros B, et al. (2009) DNA binding activity studies and computational approach of mutant SRY in patients with XY/XX SRY chimera. J Pediatr Endocrinol Metab 29: 212-218.

70. Kohler B, Lin L, Ferraz-de-Souza B, Vieacker P, Heidemann P, et al. (2008) Five novel mutations in steroidogenic factor 1 (SF1, NR5A1) in 46,XY patients with severe underandrogenization but without adrenal insufficiency. Hum Mutat 29: 913-918.
86. Gardo S, Papp Z (1974) Clinical variations of testicular intersexuality in a family. J Med Genet 11: 267-270.

87. Madden JD, Walsh PC, MacDonald PC, Wilson JD (1975) Clinical and endocrinologic characterization of patients with the syndrome of incomplete testicular feminization. J Clin Endocrinol Metab 41: 751-760.

88. Massin N, Bry H, Via L, Maione L, Constancias E, et al. (2012) Healthy birth after testicular extraction of sperm and ICSI from an azoospermic man with mild androgen insensitivity syndrome caused by an androgen receptor partial loss-of-function mutation. Clin Endocrinol (Oxf) 77: 593-598.

89. Yong EL, Loy CJ, Sim KS (2003) Androgen receptor gene and male infertility. Hum Reprod Update 9: 1-7.

90. Brinkmann AO (2001) Lessons to be learned from the androgen receptor. Eur J Dermatol 11: 301-303.

91. Boehmer AL, Brinkmann O, Bruggenwirth H, van Assendelft OC, Otten BJ, et al. (2001) Genotype versus phenotype in families with androgen insensitivity syndrome. J Clin Endocrinol Metab 86: 4151-4160.

92. Patrizio P, Leonard DG (2001) Expansion of the CAG trinucleotide repeats in the androgen receptor gene and male infertility: a controversial association. J Androl 22: 748.

93. Giwercman A, Kledal T, Schwartz M, Giwercman YL, Leffers H, et al. (2000) Preserved male fertility despite decreased androgen sensitivity caused by a mutation in the ligand-binding domain of the androgen receptor gene. J Clin Endocrinol Metab 85: 2253-2259.

94. Male Infertility Best Practice Policy Committee of the American Urological Association; Practice Committee of the American Society for Reproductive Medicine (2006) Report on evaluation of the azospermic male. Fertil Steril 86: 210-215.

95. Foresta C, Ferlin A, Gianaroli L, Dallapiccola B (2002) Guidelines for the appropriate use of genetic tests in infertile couples. Eur J Hum Genet 10: 303-312.

96. Rodien P, Mebarki F, Mowszowicz I, Chaussain JL, Young J, et al. (1996) Different phenotypes in a family with androgen insensitivity caused by the same M780I point mutation in the androgen receptor gene. J Clin Endocrinol Metab 81: 2994-2998.

97. Themmen AP, Verhoef-Post M (2002) LH receptor defects. Semin Reprod Med 20: 199-204.

98. Achard C, Courtillot C, Lahuna O, Meduri G, Soufir JC, et al. (2009) Normal spermatogenesis in a man with mutant luteinizing hormone. N Engl J Med 361: 1856-1863.

99. Basciani S, Watanabe M, Mariani S, Passeri M, Persichetti A, et al. (2012) Preserved male fertility despite decreased androgen sensitivity: identification of a new SRY gene mutation. Fertil Steril 97: 2571-2577.

100. Salehi P, Koh CJ, Pitucktechawon P, Triinh L, Daniels M, et al. (2012) Persistent Müllerian duct syndrome: 8 new cases in Southern California and a review of the literature. J Pediatr Endocrinol Metab 10: 227-233.

101. Farkkila H, Ehtisham S, Nappo S, Patel L, Hennayake S (2012) Persistent Müllerian duct syndrome: lessons learned from managing a series of eight patients over a 10-year period and review of literature regarding malignant risk from the Müllerian remnants. BJU Int 110: 1084-1089.

102. Smith-Harrison LI, Patel MS, Smith RP, Schenkman NS (2015) Persistent Müllerian duct structures presenting as hematuria in an adult: Case report of robotic surgical removal and review of the literature. Urol Ann 7: 544-546.

103. Practice Committee of the American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology (2008) The management of infertility due to obstructive azospermia. Fertil Steril 90: 121-124.
Citation: Foyouzi N, Sandberg DE (2019) Fertility in Disorders of Sex Development: Evidence and Uncertainties. J Reprod Med Gynecol Obstet 4: 015.

104. Yordam N, Alikasifoglu A, Kandemir N, Caglar M, Balci S (2001) True hermaphroditism: Clinical features, genetic variants and gonadal histology. J Pediatr Endocrinol Metab 14: 421-427.

105. Williamson HO, Phansey SA, Mathur RS (1981) True hermaphroditism with term vaginal delivery and a review. Am J Obstet Gynecol 141: 262-265.

106. Schultz BA, Roberts S, Rodgers A, Ataya K (2009) Pregnancy in true hermaphrodites and all male offspring to date. Obstet Gynecol 113: 534-536.

107. Verkaaustas G, Jauhert F, Lortat-Jacob S, Malan V, Thibaud E, et al. (2007) The long-term followup of 33 cases of true hermaphroditism: A 40-year experience with conservative gonadal surgery. J Urol 177: 726-731.

108. Schoenhaus SA, Lentz SE, Saber P, Munro MG, Kivnick S, et al. (2008) Pregnancy in a hermaphrodite with a male-predominant mosaic karyotype. Fertil Steril 90: 2016.

109. James PA, Rose K, Francis D, Norris F (2011) High-level 46XX/46XY chimerism without clinical effect in a healthy multiparous female. Am J Med Genet A 155: 2484-2488.

110. Ergun-Longmire B, Vinci G, Alonso L, Matthews S, Tansil S, et al. (2005) Clinical, hormonal and cytogenetic evaluation of 46,XX males and review of the literature. J Pediatr Endocrinol Metab 18: 739-748.

111. Fritz MA, Sporer LF (2011) Clinical Gynecologic Endocrinology and Infertility. Wolters Kluwer, South Holland, Netherlands.

112. Abusheikhla N, Lass A, Brinsden P (2001) XX males without SRY gene and with infertility. Hum Reprod 16: 717-718.

113. Boucekkine C, Toublanc JE, Abbas N, Chaabouni S, Ouahid S, et al. (1994) Clinical and anatomical spectrum in XX sex reversed patients. Relationship to the presence of Y specific DNA-sequences. Clin Endocrinol (Oxf) 40: 733-742.

114. de la Chapelle A (1981) The etiology of maleness in XX men. Hum Genet 61: 777-786.

115. Speiser PW, White PC (2003) Congenital adrenal hyperplasia. N Engl J Med 349: 776-788.

116. Gruneiro-Papendieck L, Prieto L, Chiesa A, Bengolea S, Bossi G, et al. (2004) Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod Update 10: 469-485.

117. Meyer-Bahlburg HF, Dolezal C, Baker SW, New MI (2008) Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. Arch Sex Behav 37: 85-99.

118. Hagenfeldt K, Jansson PO, Holmdahl G, Falhammar H, Filipsson H, et al. (2005) Diversity and function of mutations in p450 oxidoreductase in infantile, childhood and adolescence. Horm Res 72: 321-330.

119. Fluck CE, Tajima T, Pande y AV, Arlt W, Okuhara K, et al. (2004) Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley-Bixler syndrome. Nat Genet 36: 228-230.

120. Fukami M, Hasegawa T, Horikawa R, Ohashi T, Nishimura G, et al. (2004) Mutant type II 3 beta-hydroxysteroid dehydrogenase gene. J Clin Endocrinol Metab 89: 2127-2134.

121. Arlt W, Walker EA, Draper N, Ivison HE, Ride JP, et al. (2000) Congenital adrenal hyperplasia caused by mutant P450 oxidoreductase and human androgen synthesis: analytical study. Lancet 363: 2128-2135.

122. Huang N, Pandey AV, Agrawal V, Reardon W, Lapunzina PD, et al. (2005) Spectrum of Antley-Bixler syndrome. J Craniofac Surg 21: 1560-1564.

123. McGlaughlin KL, Witherow H, Dunaway DJ, David DJ, Anderson PJ (2010) Spectrum of Antley-Bixler syndrome. J Craniofac Surg 21: 1560-1564.

124. Alikasifoglu A, Arlt W, Draper N, Ivison HE, Ride JP, et al. (2000) Congenital adrenal hyperplasia caused by mutant P450 oxidoreductase and human androgen synthesis: analytical study. Lancet 363: 2128-2135.

125. Wang X, Pande y AV, Agrawal V, Reardon W, Lapunzina PD, et al. (2005) Diversity and function of mutations in p450 oxidoreductase in patients with Antley-Bixler syndrome and disordered steroidogenesis. Am J Hum Genet 76: 729-749.

126. Strubbe EH, Willemsen WN, Lennemann JA, Thijs CJ, Rolland R (1993) Mayer-Rokitansky-Küster-Hauser syndrome: distinction between two forms based on excretory urographic, sonographic, and laparoscopic findings. J Pediatr 123: 536.

127. Strubbe EH, Willemsen WN, Lennemann JA, Thijs CJ, Rolland R (1993) Mayer-Rokitansky-Küster-Hauser syndrome: distinction between two forms based on excretory urographic, sonographic, and laparoscopic findings. J Pediatr 123: 536.

128. Strubbe EH, Willemsen WN, Lennemann JA, Thijs CJ, Rolland R (1993) Mayer-Rokitansky-Küster-Hauser syndrome: distinction between two forms based on excretory urographic, sonographic, and laparoscopic findings. J Pediatr 123: 536.

129. Strubbe EH, Willemsen WN, Lennemann JA, Thijs CJ, Rolland R (1993) Mayer-Rokitansky-Küster-Hauser syndrome: distinction between two forms based on excretory urographic, sonographic, and laparoscopic findings. J Pediatr 123: 536.
141. Erman Akar M, Ozkan O, Aydinuraz B, Dirican K, Cincik M, et al. (2013) Clinical pregnancy after uterus transplantation. Fertil Steril 100: 1358-1363.

142. Chervenak FA, Stangel JJ, Nemec M, Amin HK (1982) Mayer-Rokitansky-Kuster-Hauser syndrome. Congenital absence of vagina. N Y State J Med 82: 23-26.

143. Strube EH, Cremers CW, Willensen WN, Rolland R, Thijn CJ (1994) The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome without and with associated features: two separate entities? Clin Dysmorphol 3: 192-199.

144. Morcel K, Guerrier D, Watrin T, Pellerin I, Leveque J (2008) [The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome: clinical description and genetics]. J Gynecol Obstet Biol Reprod (Paris) 37: 539-546.

145. Raziel A, Friedler S, Gidon Y, Ben Ami I, Strassburger D, et al. (2012) Surrogate in vitro fertilization outcome in typical and atypical forms of Mayer-Rokitansky-Kuster-Hauser syndrome. Hum Reprod 27: 126-130.

146. Petrozza JC, Gray MR, Davis AJ, Reindollar RH (1997) Congenital absence of the uterus and vagina is not commonly transmitted as a dominant genetic trait: Outcomes of surrogate pregnancies. Fertil Steril 67: 387-389.

147. Johannesson L, Jarvholm S (2016) Uterus transplantation: Current progress and future prospects. Int J Womens Health 8: 43-51.

148. Brannstrom M, Johannesson L, Dahm-Kahler P, Enskog A, Molne J, et al. (2014) First clinical uterus transplantation trial: a six-month report. Fertil Steril 101: 1228-1236.

149. Ozkan O, Akar ME, Ozkan O, Erdogan O, Hadimioglu N, et al. (2013) Preliminary results of the first human uterus transplantation from a multiorgan donor. Fertil Steril 99: 470-476.

150. Brannstrom M, Johannesson L, Bokstrom H, Kvamstrom N, Molne J, et al. (2014) Livebirth after uterus transplantation. Lancet 385: 607-616.

151. Jayachandran D, Bythell M, Platt MW, Rankin J (2011) Register based study of bladder extrophy-epispadias complex: prevalence, associated anomalies, prenatal diagnosis and survival. J Urol 186: 2056-2060.

152. Ebert AK, Reutter H, Ludwig M, Rosch WH (2009) The extrophy-epispadias complex. Orphanet J Rare Dis 4: 23.

153. Manner K, Kluth D (2005) The morphogenesis of the extrophy-epispadias complex: a new concept based on observations made in early embryonic cases of cloacal extrophy. Anat Embryol (Berl) 210: 51-57.

154. Vermeij-Keers C, Hartwig NG, van der Werff IF, et al. (1996) Embryonic development of the ventral body wall and its congenital malformations. Semin Pediatr Surg 5: 82-89.

155. Mathews RJ, Perlman E, Marsh DW, Gearhart JP (1999) Gonadal morphology in cloacal extrophy: implications in gender assignment. BJU Int 84: 99-100.

156. Woodhouse CR (1986) The management of erectile deformity in adults with extrophy and epispadias. J Urol 135: 932-935.

157. Woodhouse CR (2001) Prospects for fertility in patients born with genitourinary anomalies. J Urol 165: 2354-2360.

158. Hohenfellner R, Stein R (1996) Primary urinary diversion in patients with bladder extrophy. Urology 48: 828-830.

159. Ben-Chaim J, Jeffs RD, Reiner WG, Gearhart JP (1996) The outcome of patients with classic bladder extrophy in adult life. J Urol 155: 1251-1252.

160. Palermo G, Joris H, Derde MP, Camus M, Devroey P, et al. (1993) Sperm characteristics and outcome of human assisted fertilization by subzonal insemination and intracytoplasmic sperm injection. Fertil Steril 59: 826-835.

161. Baker Towell DM, Towell AD (2003) A preliminary investigation into quality of life, psychological distress and social competence in children with cloacal extrophy. J Urol 169: 1850-1853.

162. Deans R, Banks F, Liao LM, Wood D, Woodhouse C, et al. (2012) Reproductive outcomes in women with classic bladder extrophy: an observational cross-sectional study. Am J Obstet Gynecol 206: 491-496.

163. Shapiro E, Lepor H, Jeffs RD (1984) The inheritance of the extrophy-epispadias complex. J Urol 132: 308-310.
