Clinical Management of Disorders of Sex Development

ABSTRACT
Disorders of sex development (DSD) is an umbrella term for congenital conditions in which anatomic, gonadal, or chromosomal sex is atypical. DSD is found in 7.5% of all birth defects and 1 in 5,000 babies born worldwide have significant ambiguous genitalia. Best practices involve multidisciplinary teams, informed consent and shared decision-making with the patient and family. As a group, DSD patients are rare and therefore clinically challenging. Primary care providers, family medicine physicians, and pediatricians are the foundation for patients’ medical care and therefore play a key role in the initial diagnosis, guidance, coordination of care, and long-term management.

KEYWORDS: Disorders of sex development, intersex, gender identity, sex differentiation, ambiguous genitalia

Disorders of Sex Development
Disorders of sex development (DSD) encompasses a variety of medical conditions of the reproductive tract system. DSD is defined as congenital conditions in which development of anatomic, gonadal, or chromosomal sex is atypical.1 Historically, these individuals with ambiguous genitalia have been termed “hermaphrodites”. Over the last few decades, there have been dramatic changes in nomenclature, perspectives, gender assignments, and medical and surgical management. As a group, DSD patients are rare and therefore clinically challenging. Primary care providers, family medicine physicians, and pediatricians are the foundation for patients’ medical care and therefore play a key role in the initial diagnosis, guidance, coordination of care, and long-term management.2,3

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Brief History of DSD

In the 1950s, John Money defined gender development and his philosophy included gender neutrality at birth; gender identity was based upon upbringing and environmental influences regardless of chromosomal, gonadal, or hormonal sex. In 2005, the “Chicago Consensus” was developed at The International Conference of Management of Intersex, giving rise to a new era for intersex management. The consensus emphasized the need for a multidisciplinary approach as gender identity is complex and influenced by hormonal and environmental factors, genetics, and molecular biology. The consensus statement, recently updated in 2016, also redefined DSD nomenclature due to negative connotations of its historical terms, encouraged transparency, and recommended further support, research, and education.

Sexual Differentiation

Sex differentiation is a complex process influenced by the X and Y sex chromosomes, transcription regulators, and hormones. When the sex-determining region on the Y chromosome, the SRY gene, is present, the bipotential gonads differentiate into testes during week seven of gestation. Testosterone, produced by the testicular Leydig cells, leads to the development of the Wolffian duct structures, including the epididymis, vas deferens, seminal vesicles, and the ejaculatory ducts. Sertoli cells of the testis will produce anti-Müllerian hormone (AMH), which suppresses the development of Müllerian structures, including the oviducts, uterus, cervix, and upper vagina. In the absence of the SRY gene, the bipotential gonads develop into ovaries and subsequently Wolffian structures disappear.

Differentiation of the external genitalia occurs through exposure to androgens during weeks 8 to 12 of gestation. Testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase. DHT is the primary androgen that stimulates prostate development, penile enlargement, descent of testicles, and fusion of the labioscrotal folds to form the scrotum. Estrogen encourages the formation of the lower part of the vagina and the labioscrotal folds become the vulva. In this complex development, a chromosomal or endocrine disruption can manifest as DSD, with presentation from mild to severe atypical genital phenotypes.
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Epidemiology
DSD accounts for 7.5% of all birth defects.7 While many patients are diagnosed at birth due to visually apparent anatomical variances, others may never be diagnosed or diagnosed at later stages. The incidence of atypical external genitalia that is sufficient to warrant genetic and endocrine studies is estimated to be 1 in 5,000 births.8,9

Clinical Evaluation and Diagnosis
Physical exam findings that prompt a DSD work-up in neonates include bilateral non-palpable testes, hypospadias in combination with a unilateral undescended or non-palpable testis, clitoral hypertrophy, foreshortened vulva with a single urogenital tract opening, and an inguinal hernia with a palpable gonad in a phenotypic female infant.10 In older patients, unrecognized genital ambiguity, female inguinal hernia, delayed puberty, female virilization, primary amenorrhea, phenotypic male breast development, and cyclical gross hematuria indicative of menstruation in a phenotypic male are also signs for DSD evaluation.11 Initial evaluation of DSD includes a thorough history, physical exam, evaluation of sex chromosomes using karyotype and fluorescence in situ hybridization (FISH), and assessment of internal organs by abdominopelvic ultrasonography.

Table 1: Current Terminology versus Historical Terminology

<table>
<thead>
<tr>
<th>Current Terminology</th>
<th>Historical Terminology</th>
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<tbody>
<tr>
<td>Disorders of Sex Development</td>
<td>Hermaphrodite</td>
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<tr>
<td></td>
<td>Intersex*</td>
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<td>* Some patients may still identify as “intersex” Alternatively, some may prefer differences, divergence, or variation of sex development</td>
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<tr>
<td>46, XX DSD</td>
<td>Female pseudohermaphrodite</td>
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<td>Overvirilization of an XX female</td>
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<td>Masculinization of an XX female</td>
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<tr>
<td>46, XY DSD</td>
<td>Male pseudohermaphrodite</td>
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<td>Undervirilization of an XY male</td>
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<tr>
<td></td>
<td>Undermasculinization of an XY male</td>
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<tr>
<td>Ovotesticular DSD</td>
<td>True hermaphrodite</td>
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<td>46, XX testicular disorder</td>
<td>XX male</td>
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<td></td>
<td>XX sex reversal</td>
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<tr>
<td>46, XY complete gonadal dysgenesis</td>
<td>XY sex reversal</td>
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</table>
**Family History**

History includes obtaining detailed assessment of consanguinity, fertility complications, stillbirths, miscarriages, genital abnormalities, hernias, disorders of puberty, genital surgery, neonatal deaths, and steroid replacement. Additional prenatal history should include medication use, substance exposure, and virilization of the mother. Most DSD conditions are either autosomal recessive or sporadic.

**Physical Exam**

Physical exam includes vitals, general physical exam, and a genitourinary exam. The groin and scrotal or labial folds should be examined to determine the presence of gonads. Undescended testes may be located in the inguinal canal, superficial inguinal pouch, upper scrotum, or rarely, in the femoral or perineal region. Though suprapubic fat may make it difficult, it is important to evaluate for micropenis (stretched penile length = <2.5 standard deviations of the mean for the age of the patient). Inspect for hypospadias, the incomplete fusion of the urethral folds on the ventral penis. In adolescents, secondary sexual characteristics such as gynecomastia or clitoral enlargement should be assessed.

**Diagnostic Workup**

With the increased use of fetal monitoring, prenatal diagnosis of DSD is more frequent. Karyotyping with FISH is most useful when ambiguous genitalia is suspected. Other valuable diagnostic tools performed by a pediatric endocrinologist may include copy number variants associated with known DSD genes, high coverage chromosomal microarray analysis, serum electrolytes, and steroid metabolites such as testosterone, DHT, and 17-hydroxyprogesterone. Abdominopelvic diagnostic imaging such as ultrasound or magnetic resonance imaging can evaluate the location of gonads and internal genital structures.

**DSD Classification**

Currently the three classifications within DSD are (1) 46, XX DSD, (2) 46, XY DSD, and (3) chromosomal DSD.

I. 46, XX Disorders of Sex Development

Virilization of the female fetus was historically termed “female pseudohermaphroditism.” These DSD conditions arise from disorders of gonadal or ovarian development and androgen excess. The excess may be from an exogenous source or secreted by the fetus and causes virilization; the labioscrotal folds fuse and the clitoris enlarges if the exposure occurs between weeks 8 and 14 of gestation. Diagnostic concern is to exclude ovarian or adrenal androgen-secreting tumor, congenital hyperplasia, or polycystic ovarian syndrome post-puberty.
**Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders in the steroidogenic pathway that leads to increased androgen production. 95% of CAH cases are due to 21-hydroxylase deficiency (21OHD). The incidence is approximately 1 in 15,000 live births. Classic 21OHD CAH presents in females with virilization such as clitoromegaly or labial fusion. Males present with enlarged phal-ulus or normal genitalia in males. Nonclassic 21OHD CAH is associated with normal genitalia and late onset of androgen excess, including hirsutism and precocious puberty. Other common causes of CAH include 11-hydroxylase deficiency and 3-β-hydroxysteroid dehydrogenase type 2 deficiency.

Historically, gender assignment for 46, XX CAH patients were female due to fertility potential. However, outcome studies have shown that a male assignment is an appropriate consideration if the 46, XX patient is severely virilized. Early surgery is not mandatory in the absence of anatomy-causing medical problems and may be delayed until the patient can participate in the discussion. In the long-term, it is important to monitor childhood growth and pubertal development, provide genetic counseling to families and patients, optimize fertility, and prevent osteoporosis due to lifelong glucocorticoid therapy. CAH is also associated with obesity, insulin resistance, and hypertension. Females with CAH may face the challenges of impaired sexual function and depressive symptoms.

**II. 46, XY Disorders of Sex Development**

Undervirilized 46, XY patients were historically termed “male pseudohermaphrodites.” These conditions arise from disorders of gonadal or testicular development and impaired androgen synthesis or action.

**5-Alpha-Reductase Deficiency**

5α-reductase type 2 deficiency (5α-RD2) is a rare autosomal recessive disorder in 46, XY individuals caused by a mutation in the SRD5A2 enzyme that converts testosterone to DHT. The prevalence is unknown, however, the highest prevalence occurs in the Dominican Republic, Lebanon, and Papua New Guinea. Virilization correlates with the severity of the mutation. Laboratory findings include normal or elevated testosterone levels and low DHT levels. Clinical presentations range from external female genitalia, female genitalia with clitoromegaly, isolated microphallus, and microphallus associated with hypospadias. During puberty, the testes produce more testosterone, and individuals will undergo male-like puberty such as phallic growth, testicular descent, development of pubic hair,
increased muscle mass, deepening of voice, and growth spurt.

Given the high rate of male gender identity post-puberty, the historical sex assignment of female during infancy is no longer recommended. Male assignment is recommended as 60% of those with 5α-RD2 will later identify themselves as male.9 For those caring for 5α-RD2 men, infertility may be an issue due to low sperm count, but pregnancy can be achieved with the aid of intrauterine insemination.24

17-β-Hydroxysteroid Dehydrogenase Deficiency

17-β-hydroxysteroid dehydrogenase type 3 deficiency (7β-HSD-3) is a rare autosomal recessive disorder with mutations in the enzyme that converts androstenedione into testosterone in the male testis.25 17β-HSD-3 is estimated to affect 1 in 147,000 live births.26 The diagnosis is made by a βHCG-stimulated ratio of testosterone to androstenedione that is less than 0.8, though diagnosis should be confirmed with genetic testing.27 Clinical presentation may be subtle, as phenotypes range from external female genitalia with labial fusion and blind-ended vagina to microphallus with hypospadias.28 If undiagnosed during infancy, patients may present in adolescence with severe virilization and primary amenorrhea. Male gender identity occurs in at least 50% of 17β-HSD-3 individuals, therefore current recommended gender of rearing is male.9

Androgen Insensitivity Syndrome

X-linked mutations of the androgen receptor lead to hormone resistance despite appropriate hormone secretion. Incidence is approximately 1 in 20,000 individuals.29 Those with complete androgen insensitivity syndrome (CAIS) present with female phenotype and shallow, blind ending vagina with no uterus or oviducts.30 During puberty, testosterone will aromatize to estrogen, leading to breast growth. Classic signs of CAIS are inguinal or labial swellings due to undescended testes during infancy or primary amenorrhea during adolescence.31 Those with partial or mild androgen insensitivity may have a wide spectrum of presentation, including micropenis, hypospadias, bifid scrotum, or in some cases, female-appearing external genitalia and clitoromegaly.

With a positive family history, AIS can be prenatally tested during weeks 9-12 of gestation with chorionic villus sampling or amniocentesis by week 16. For neonates, biochemical testing includes serum LH, FSH, testosterone, inhibin, and AMH. In children or adults, a human chorionic gonadotropin stimulation test and a LH releasing hormone stimulation rules out testosterone biosynthesis defect and 5α-reductase deficiency.32 Genetic testing of the androgen receptor gene can confirm an AIS diagnosis.
CAIS infants are assigned female with few reports of gender dysphoria. In contrast, the phenotype and gender variability of incomplete AIS poses multiple challenges in diagnosis, sex assignment, and surgical timing. Long-term care for AIS patients should include close monitoring for those at risk of gonad tumor development and evaluation of gender identity.

### III. Chromosomal DSD

Chromosomal DSD are numeric sex chromosome anomalies.

**Ovotesticular DSD**

Historically termed “true hermaphrodites,” ovotesticular DSD patients possess both ovarian tissue and testicular tissue. The incidence is estimated to be 1 in 20,000. Diagnosis requires surgical biopsy of gonadal tissues for confirmation of both tissues. Patients may have both gonadal tissues bilaterally or an ovotestis unilaterally. Though most patients are infertile, pregnancy has been observed in patients raised as female.

**Mixed gonadal dysgenesis**

Also known as 45,X/46,XY mosaicism or 45,X/46,XY chimerism, patients with mixed gonadal dysgenesis have structural or numerical anomalies of sex chromosomes that lead to incomplete or defective formation of gonads. Phenotypes of gonadal dysgenesis encompasses a wide spectrum. Individuals are mostly reared male due to the presence of Y chromosome and modest virilization. An important component in the care for mixed gonadal dysgenesis patients who have a Y chromosome is monitoring for gonadal malignancies; decisions regarding gonadectomy should be tailored to each patient based on the underlying diagnosis and risk of malignancy.

### IV. 46, XY and 46, XY with Genital Anomalies

Individuals may also present with genital malformations when chromosomal, gonadal, and sex hormones are fully functional. Though the following physical findings will prompt a DSD workup, the etiology may be unrelated to DSD and associated with other diagnoses.

**Micropenis:** Micropenis is defined as stretched penile length <=2.5 of standard deviation from the mean for the age of the patient. Micropenis is a common DSD finding, though etiologies may also be due to natural variance, idiopathic, hypogonadotropic hypogonadism due to pituitary or hypothalamic insufficiency, or hypergonadotropic hypogonadism due to primary testicular insufficiency.

**Hypospadias:** Hypospadias is a birth defect in which the urethral opening is located on the ventral aspect of the penis. It is a common birth defect with an incidence of
1 of 250 in males, and associated with chordee.\(^3^{6}\) Severity of hypospadias has strong positive correlation with an intersex state.\(^3^{7}\)

**Cryptorchidism:** Undescended testis is defined as a testis that cannot be manipulated into the bottom of the scrotum by 12 weeks of age, and may be bilateral or unilateral. Up to 4.5% of newborn males have cryptorchidism, with higher rates in preterm newborns (30-45%).\(^3^{8}\) Rates fall to 1-2% by 12 weeks after term.\(^3^{9}\) Patients with both hypospadias and a unilateral undescended or non-palpable testis prompts a DSD workup.

**Clitoromegaly:** Clitoromegaly is the hypertrophy of the clitoris, usually occurring during fetal development, puberty, or later in adulthood. Clitoral abnormalities not associated with virilization syndromes are rare.

**Müllerian/vaginal agenesis (also known as Mayer-Rokitansky-Kuster-Hauser Syndrome):** Patients with MRKH have disorders of the reproductive tract, including vaginal aplasia or other mullerian duct abnormalities such as a small, misshaped, or missing uterus. They often present with primary amenorrhea, despite normal appearing external genitalia and normal secondary sexual characteristics. Individuals may also have renal or vertebral abnormalities. Guidance and support on disclosure to friends and partners can help alleviate patients’ recurring anxieties.\(^4^{0}\) Patients may elect pressure dilation or secondarily surgical augmentation if increased vaginal length is a goal.

### Approach to Management, Counseling and Follow-up

A multidisciplinary care approach with shared decision-making, full disclosure, and genital surgery focused on function are the current best practices in DSD care. Understandably, a DSD diagnosis may be highly distressing to patients and their families. Gender satisfaction correlates to positive parental and social support.\(^4^{8}\) Therefore, initiating the connection to other patients or families and recommending support groups can alleviate isolation, normalize a DSD diagnosis, and encourage positive adaptation.\(^4^{6}\)

The Accord Alliance, a leading DSD advocacy organization, recommends that the ideal DSD medical team includes pediatric subspecialists in endocrinology, surgery and/or urology, psychology or psychiatry, gynecology, genetics, neonatology, and if available, social work and medical ethics.\(^4^{1}\) Regardless of the team members in place, psychosocial support to both the family and patient is an imperative part of the comprehensive care.

Psychosocially, new evidence suggests intersex patients cope well with DSD overall, with no significant reduction in quality of life.\(^4^{2}\) No differences in psychosocial well-
being were detected between men with DSD and reference men. In contrast, there have been studies that have shown elevated levels of fatigue, attention, memory, and emotional and behavioral problems in females with DSD. In general, individuals with DSD do not show increased gender dysphoria, but may encounter more difficulties in partnership and sexual relationships.

Conclusions
While current nomenclature and management are still imperfect, the greatest challenges remain in furthering our understanding of gender development and improving the timing and indication for definitive therapies. As DSD management continues to transform, we hope patient outcomes will improve as we gain more knowledge of these conditions.

SUMMARY OF KEY POINTS

The most common causes of DSD are congenital adrenal hyperplasia (CAH) and mixed gonadal dysgenesis, constituting approximately half of all DSD cases discovered in newborns.

Initial evaluation of DSD should include a thorough history, physical exam that includes assessment of genital anatomy, evaluation of sex chromosomes using karyotype and fluorescence in situ hybridization, and assessment of internal organs by abdominopelvic ultrasonography.

The three classifications within DSD are 46, XX DSD (disorders of gonadal or ovarian development and androgen excess), 46, XY DSD (disorders of gonadal or testicular development and impaired androgen synthesis or action), and chromosomal DSD (numeric sex chromosome anomalies).

Overlooked DSD diagnosis can have the fatal consequence of adrenal crisis due to CAH; phenotypic males with CAH do not present with ambiguous genitalia and therefore adrenal crisis may go undetected at birth.

CLINICAL PEARLS

Physical exam findings that should prompt a DSD workup in neonates include bilateral non-palpable testes, hypospadias in combination with a unilateral undescended testis or non-palpable testes, clitoral hypertrophy, foreshortened vulva with a single urogenital tract opening, and an inguinal hernia with a palpable gonad in a phenotypic female infant.

Initiating the connection to other patients or families and recommending support groups can alleviate isolation, normalize a DSD diagnosis, and encourage positive adaptation.
## Resource Table:

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<tr>
<th>ORGANIZATION</th>
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<tr>
<td>Accord Alliance</td>
<td>Promote comprehensive and integrated approaches to care that enhance the health and well-being of people and families affected by DSD by fostering collaboration among all stakeholders.</td>
<td>accordalliance.org</td>
</tr>
<tr>
<td>Association for X and Y Chromosome Variations</td>
<td>Help individuals with one or more extra X and/or Y chromosomes and their families to lead fuller, more productive lives. Formed by the merger of KS&amp;A (formerly Klinefelter Syndrome and Associates) and AAKSIS (American Association for Klinefelter Syndrome Information and Support).</td>
<td>axysgenetic.org</td>
</tr>
<tr>
<td>Androgen Insensitivity Syndrome Support Group</td>
<td>Provide information and support to young people, adults and families affected by XY-female conditions such as complete and partial AIS. Also support those affected by Swyer’s Syndrome (XY Gonadal Dysgenesis), 5-alpha Reductase Deficiency, Leydig Cell Hypoplasia, Mayer-Rokitansky-Kuster-Hauser (MRKH) Syndrome, Mullerian Dysgenesis, Mullerian Duct Aplasia, Vaginal Atresia, and other related conditions.</td>
<td>aissg.org/INDEX.HTM</td>
</tr>
<tr>
<td>CARES Foundation</td>
<td>Improve the lives of the Congenital Adrenal Hyperplasia community and seek to advance quality health care through support, advocacy, education and research.</td>
<td>caresfoundation.org</td>
</tr>
<tr>
<td>Disorders of Sex Development</td>
<td>An on-line information and support resource for families with children, teens and young adults who have a DSD. It brings together user-friendly information on the medical management and decision-making in DSD, with psychological support, and sensitive and practical peer support.</td>
<td>dsdfamilies.org/index.php</td>
</tr>
<tr>
<td>Genetic and Rare Diseases (GARD)</td>
<td>A program of the National Center for Advancing Translational Sciences (NCATS) to provide access to current, reliable, and easy to understand information about rare or genetic diseases in English or Spanish.</td>
<td>rarediseases.info.nih.gov/GARD</td>
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<tr>
<td>Hypospadias &amp; Epispadias Association</td>
<td>Founded for the education and support of people born with hypospadias or epispadias, their families, and loved ones.</td>
<td>heainfo.org</td>
</tr>
<tr>
<td>Intersex Society of North American (ISNA)</td>
<td>Devoted to systemic change to end shame, secrecy, and unwanted genital surgeries for people born with an anatomy that someone decided is not standard for male or female.</td>
<td>isna.org</td>
</tr>
<tr>
<td>Magic Foundation</td>
<td>Provide support services for the families of children afflicted with a wide variety of chronic and/or critical disorders, syndromes and diseases that affect a child's growth. Reduce the emotional and physical trauma caused by growth disorders, resulting in healthier, happier children and consequently, adults.</td>
<td>magicfoundation.org</td>
</tr>
<tr>
<td>Müllerian Agenesis</td>
<td>For women with Mayer-Rokitansky-Kuster-Hauser Syndrome. Create a supportive community that partners with health care professionals to increase awareness and empower women of all ages with MRKH to feel beautiful, just as they are.</td>
<td>mrkh.org; beautifully oumrkh.org</td>
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Suggested reading:


References

Post-test Quiz

Members of the College of Family Physicians of Canada may claim MAINPRO-M2 Credits for this unaccredited educational program.


