Chapter 52
Disorders/Differences of Sex Development (DSD)

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Abstract Disorders of sex development (DSD), sometimes called *differences* of sex development are conditions that affect reproductive organs and can include alterations of chromosomal, metabolic, gonadal or anatomical function. Some of the conditions result in genital ambiguities that are noted in newborns and some are not discovered until adolescence. There have been rapid shifts in the understanding of these conditions with strong support from advocacy organizations allowing more self-direction from patients affected by DSD. A multidisciplinary team is essential to the comprehensive care these patients will need over their lifetime and the team should include psychosocial providers, endocrinologists, geneticists, gynecologists, social workers and surgeons. Peer support is also a key part of the care, especially during adolescence, and attention to age-appropriate education and cultural sensitivity can customize the care for each individual patient and their needs. Fertility issues should be a part of the discussion from an early age, especially when decisions are being made about irreversible surgery and/or gonadectomy. Shared decision making tools have been developed to help address all of these issues for individuals affected by DSD.

Keywords Disorders of sex development · Congenital adrenal hyperplasia · Androgen insensitivity syndrome · Vaginal agenesis · Mayer-Rokitansky-Kuster-Hauser syndrome · Mixed gonadal dysgenesis

1. What are the categories of DSD?

The 2006 consensus statement from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology helped defined nomenclature and established the term disorder of sex development [1]. Table 52.1

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Table 52.1 Categories of disorders/differences of sex development [2]

46, XX DSD	46, XY DSD	Gonadal ambiguities or absence	Anatomical/developmental anomalies
Congenital adrenal hyperplasia	Androgen insensitivity syndrome (AIS)	Mixed gonadal dysgenesis (MGD) or chromosomal mosaicism (45, X/46, XY)	Cloacal anomalies
	Partial AIS		Bladder exstrophy
	Complete AIS		
21-hydroxylase deficiency	Insufficient testosterone production	Pure gonadal dysgenesis (46, XX or 46, XY)	Caudal regression syndrome
11-hydroxylase deficiency	Inability to convert testosterone to dihydrotestosterone	Ovotesticular DSD (46, XX or 46, XY)	VACTERL synd
3β-hydroxysteroid deficiency			Persistent mullerian duct syndrome
Aromatase deficiency			Mayer-Rokitansky-Kuster-Hauser syndrome/vaginal agenesis
			Urogenital sinus

shows the categories which are based on chromosomal makeup and anatomical findings.

2. **What is the current nomenclature used to describe patients with DSD?**

Patients with DSD are described by the chromosomal makeup, e.g. XY, DSD, as well as their descriptive diagnosis, e.g. complete androgen insensitivity. The word 'differences' has been suggested instead of 'disorders.' Older terms that are not used include hermaphrodite, pseudohermaphrodite and the use of the word 'virilized' is discouraged. Describing an individual as intersex or as having intersex traits has become more acceptable.

3. **How is gender of rearing determined?**

Most infants with DSD will have a gender assigned that is in line with what is expected as they grow but in some cases a gender of rearing may be deferred.

4. **When are patients with DSD diagnosed?**

Diagnosis can be made prenatally when there is discordance between a cell-free fetal DNA test and the appearance of the genital structures on ultrasound. More frequently, newborns with genital differences will be identified postnatally. Adolescents can also be diagnosed with DSD during a work up for amenorrhea.

5. **What is the most common DSD?**

Congenital adrenal hyperplasia is the most common DSD with a worldwide incidence estimated to be 1 in 14,000–15,000 live births.

6. **What is involved in the evaluation of a newborn with a DSD?**

Newborns with genital differences should be evaluated by a pediatrician or neonatologist with the goal of ruling out any life-threatening conditions such as

salt-wasting congenital adrenal hyperplasia or any associated cardiac or renal anomaly. Consultation with a multidisciplinary team including genetics and endocrinology is essential. Labs and imaging in the nursery can help narrow the differential.

7. **Are these diagnoses picked up prenatally?**

Evaluation of the gender of a fetus involves ultrasound imaging of the genitalia and, in some cases, cell-free fetal DNA detected in the mother's blood stream. There can be limited views of the fetus due to positioning. If there is a concern for genital ambiguity on prenatal imaging, referral to a center with a DSD clinic is indicated.

8. **Are there any prenatal therapies available for DSD?**

For families with a previous history of congenital adrenal hyperplasia, a possible therapy for future pregnancies involves early steroid therapy for the mother to mitigate the effects of excess androgens and potentially limit the virilizing effects on the genitalia of the fetus. This therapy has come under question due to the need to treat all fetuses, even when it is not known if the fetus is affected by CAH. The steroids may be related to cognitive deficits long term. [3]

9. **What types of chromosomal differences are seen in patients with DSD?**

Patients with DSD can have normal chromosomes that do not match their phenotypic sex or gender identity. They can also have a chromosomal mosaicism. Providers should first order a standard karyotype and depending on the results, more sophisticated studies should be pursued and that may include a chromosomal microarray.

10. **What medical and anatomical findings are expected on a newborn with congenital adrenal hyperplasia** (CAH)**?**

Infants with CAH can be expected to have elevated levels of hormones depending on which enzyme deficiency is present. In the most common form of the disease, 21-hydroxyprogesterone deficiency, the excess androgen is 17-beta-hydroxyprogesterone. This level should be checked in an infant with XX chromosomes and genital difference, especially in the setting of an enlarged clitorophallic structure and nonpalpable gonads.

11. **What is the medical and surgical management of a newborn with CAH?**

Initial medical management of a newborn diagnosed with CAH is support in terms of treatment with steroids. Infants are given a form of cortisol called hydrocortisone. Patients with classic CAH also require fludrocortisone to replace aldosterone. No surgical intervention is indicated in a newborn with CAH unless there is urinary obstruction from the urogenital sinus, which is rare.

12. **How does a shared decision making process affect the care of a newborn or adolescent with DSD?**

Patient centered care has been an initiative of recent efforts to decrease complications and costs in medicine. Families of patients with DSD are suited to this type

of decision making since many crossroads in care are encountered that require careful education and weighing of options. Involving the patients themselves in any irreversible decision is especially important.

13. **What other diagnoses are seen in newborns?**

Other that CAH, infants can have genital difference due to chromosomal mosaicism or mixed gonadal dysgenesis. This can result in a variable upper reproductive tract anatomy that can included dysgenetic gonads or discordant gonads (testis or ovotestis on one side and ovary or streak gonad on the other) and variable lower reproductive tract anatomy including an enlarged clitorophallic structure and urogenital opening. Many infants with cloacal anomalies also have genital differences.

14. **Which DSDs present in older patients?**

Part of the workup of primary amenorrhea in an adolescent teen may reveal chromosomal or anatomical reasons that end up being a DSD. Patients with androgen insensitivity syndrome (AIS) will be found to have XY chromosomes and retained testicles. Patients with vaginal agenesis or Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome are often diagnosed in this time period and will be found to have XX chromosomes.

15. **What is the medical and anatomical evaluation of an older child with DSD?**

Older patients should be seen by a DSD team and undergo a medical evaluation that includes basic labs and hormone levels, chromosomal studies, and imaging to evaluate upper and lower reproductive tract anatomy. A complete psychosocial evaluation can guide the patient's understanding of the diagnosis and desired goals.

16. **How are the gonads managed in an adolescent with androgen insensitivity syndrome (AIS)?**

Historically, the gonads or retained testicles were removed after AIS patients reached puberty due to a perceived risk of malignancy. That risk may have been overstated and now options including gonad retention and/or preservation of genetic material for fertility should be discussed. Some patients may wish to avoid gonadectomy so they can continue to have their endogenous hormone production as long as possible. [4]

17. **If gonadectomy is perfomed in a patient with AIS, what are recommendations for hormone replacement?**

Patients with AIS who opt for gonadectomy would benefit from hormone replacement with estrogen and some patients have sought testosterone supplementation as well. Hormone levels can be followed and the goal of therapy should be to avoid symptoms that mimic those of post-menopausal women.

18. **How is partial androgen insensitivity syndrome (PAIS) different from complete androgen insensitivity syndrome (CAIS)?**

PAIS is a diagnosis of exclusion in that patients may not have a detectable defect in the androgen receptor gene. Anatomy is variable but usually involves genital differences, a urogenital sinus and/or utricle, and retained gonads consistent with testicles. Malignancy risk is unknown for retained gonads.

19. **What is Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome and how is it managed?**

Patients with MRKH or vaginal agenesis have an XX chromosomal makeup and normal ovaries. The uterine anatomy is variable and they may have rudimentary uterine tissue but no vagina. A dimple of hymenal tissue on the perineum is usually present. Diagnosis is made by physical exam, chromosome and/or lab evaluation, and ultrasound imaging of the upper reproductive tract anatomy.

20. **What is the treatment for adolescents and young adults with MRKH?**

Decision making tools can be helpful in guiding patients with MRKH. Understanding the diagnosis and options for fertility is the first step and vaginal anatomy is assessed when the patient is ready. In most cases, nonoperative therapy with progressive perineal dilation can establish a vaginal canal. Coital dilation and reconstructive vaginoplasty are other options [5].

21. **What are options for patients with mixed gonadal dysgenesis (MGD) or chromosomal mosaicism?**

Due to the variable nature of the chromosomal makeup and upper/lower reproductive tract anatomy in patients with DSD, careful consideration should be made to delaying irreversible procedures. CAH should be ruled out since anatomy can be similar but patients with CAH may need steroid therapy.

22. **How are the gonads managed for patients with MGD or chromosomal mosaicism?**

The malignancy risk may relate to the amount of virilization and families of patients with chromosomal mosaicism should be educated on ways to perform surveillance on retained gonads. Allowing the patient to make any decisions about reconstructions, if desired, is ideal.

23. **What psychosocial support is suggested for patients and families affected by DSD?**

An essential part of the DSD team is the psychosocial provider. Psychology support as well as clinical counselor and social workers can help monitor anxiety, depression, adjustment disorder, body self-image issues and help recommend therapies that build confidence and resilience.

24. **How does public opinion and changes in the way society sees gender affect the care of patients with DSD**

Attention from the media toward patients with gender differences can be a positive force that helps society accept a wide range of gender identities. Providers can be part of a process that allows patient autonomy and self-direction while emphasizing medical and anatomical priorties.

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