Disorders of Sexual Differentiation

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Last Updated:

Wednesday, January 18, 2023

1. Introduction

In 2006 a panel of professionals, parents and affected individuals collaborated to generate a consensus statement on management of individuals with intersex conditions[1] **A multidisciplinary model of care was emphasized, and new nomenclatur was introduced with the goal of minimizing pejorative terms. This updated nomenclature has become a common and specific language for the medical community. Disorders of Sex Development (DSD)** (also called Disorder of Sexual Differentiation), was preferred over intersexuality and the prior hermaphroditism (**Table 1**). A review of 60 European DSD centers showed that a majority implemented policies and procedures in accordance with the recommendations issued by the 2006 Consensus Group, representing a change in practice with the collaborative goal of improved patient care.[2]

Since the nomenclature update, members of the affected community have expressed dissatisfaction with nomenclature that suggests a *disorder*. A small sample study of the Androgen Insensitivity Syndrome–DSD Support Group showed that affected parents have negativ views about the DSD terminology commonly used by medical professionals.[3] A follow up study indicates lack of consensus among a clinic population about preferred terminology.[4] Additionally some patients with congenital adrenal hyperplasia (CAH) and their parents prefer to separate CAH from DSD, viewing CAH as an endocrine condition rather than a DSD.[5] There is also controversy about which forms of hypospadias should be considered under the DSD umbrella.[6] **While there is no clear consensus about terminology, individuals may prefer use of DSD, difference of sex development, intersex or a specific diagnosis and re-evaluation of current nomenclature, i collaboration with affected individuals, is needed**

1.1 Key words

Disorder of sex development, difference of sex development, dysgenesis, gender, gender identity, genital ambiguity (atypia), gonad, intersex, ovotestis, sex of rearing

2. Definition

The collection of diagnoses referred to as DSD involve discordance among three processes: **chromosomal**, **gonadal**, or **phenotypic s determination**. Human sex development occurs in an organized, sequential manner.[7,8,9,10,11,12,1,13,14,15,16,17,18,19,20] Chromosomal sex is established at fertilization, which then directs the undifferentiated gonads to develop into testes or ovaries. Phenotypic sex results from t differentiation of internal ducts and external genitalia under the influence of hormones and transcription factors. **Sexual differentiation regulated by more than 50 different genes on both the sex chromosomes and autosomes.**[11,12,18,19]

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Table 1: DSD Nomenclature

Previous Nomenclature	Updated Nomenclature
Intersex	DSD
Female pseudohermaphrodite	46,XX DSD
Gonadal Dysgenesis	Gonadal Dysgenesis
True hermaphrodite	Ovotesticular DSD
Male pseudohermaphrodite	46,XY DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

3. DSD Categories

(see reference 14)

3.1 46,XX DSD

3.1.1 Definition

46,XX DSD (previously **female pseudohermaphroditism**) is the most common DSD.[10,18] There are three major categories, as outlined the 2006 Consensus Statement.[14]

- *Disorders of gonadal development (e.g., ovotesticular DSD, 46, XX testicular DSD)*
- *Androgen excess (e.g., congenital adrenal hyperplasia)*
- *Other (typically anatomic abnormalities such as cloacal exstrophy, vaginal atresia)*

Of these, androgen excess is the most frequent, and is the focus of the discussion below. The female fetus is masculinized due to overproduction of adrenal androgens and precursors (endogenous due to enzyme deficiency in steroid biosynthesis pathway or exogenous maternal).[19]

3.1.2 Presentation

The ovaries and Müllerian derivatives are normal. Masculinization is limited to the external genitalia and urogenital sinus. The female fet is masculinized if exposed to androgens; the degree of masculinization is determined by the stage of differentiation at the time of exposu

3.1.3 Pathophysiology

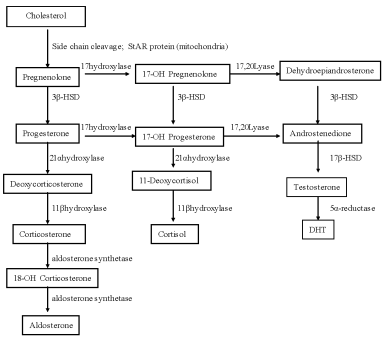

Figure 2: The steroid biosynthetic pathway.

Figure 1: Steroid Biosynthetic Pathway

Congenital adrenal hyperplasia (**CAH**) accounts for the majority of 46,XX DSD. Inactivating or loss of function mutations in five genes involved in steroid biosynthesis cause CAH: **CYP21**, **CYP11B1**, **CYP17**, **HSD3B2**, and **StAR** (**Figure 1**).

3.1.4 Evaluation

Labs include karyotype, serum electrolytes, 17OH-progesterone, T, LH, and FSH levels. If the 17OH-progesterone level is elevated, 11-deoxycortisol and DOC levels differentiate 21α-hydroxylase deficiency from 11β-hydroxylase deficiency. **21α-hydroxylase deficien accounts for most cases of CAH (>95%).** 17OH-progesterone can be inaccurate before ~36 hours of life, and salt wasting typically occurs at about 1 week of life, so timing of laboratory testing is important. Pelvic ultrasound identifies the uterus. Genitogram or cystoscopy evaluates the urogenital sinus including the confluence of the urethra and the vagina.

3.1.5 Management

Initial treatment is correction of dehydration and salt loss by electrolyte and fluid therapy with mineralocorticoid replacement. Glucocorticoid replacement is added upon confirmation of the diagnosis. Historically and even as of the date of this curriculum update, surgical intervention has been common in the management of infants. Controversy exists on the timing of surgery (infant, toddler, or adolescent), with consideration of impact of irreversible procedures on children before the age of assent/consent. This decision may evolve for the patients and families we care for over the coming years. The learner should remain abreast of current controversies and w as local and global perspectives.

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The basic surgical concepts are included here for education of the learner. Surgical decisions are by consensus of the team, fully involvi the parents, and with input from the patients when developmentally appropriate. **In CAH, surgery has three main components: urethroplasty and vaginoplasty to create separate orifices and externalize and enlarge the vaginal opening; clitoroplasty with reduction of the size of the masculinized clitoris and creation of a clitoral hood; feminizing vulvoplasty / labioplasty**(**AUA Upda Series**: **Early genital surgery in children with disorders of sex development: concerns, consents, conundrum. Disandro M, Vol Lesson 6, 2016**). Infrequently, persistence of an uncorrected urogenital sinus can be associated with urinary tract infection, painful fluid collection in the vagina and/or uterus, and peritonitis due to retrograde flow. Surgical techniques continue to be revised with the goals of optimizing the feminine cosmetic result while preserving sensation and function. Many years ago, clitorectomy was performed and is certainly no longer supported. Concealment by burying the clitoral tissue (clitoral recession) resulted in pain and is also not recommended. Contemporary techniques of reduction clitoroplasty, such as nerve sparing ventral clitoroplasty involve preservation of the dorsal neurovascular tissue while debulking the corporal bodies and reseating the glans clitoris on the proximal aspect of the clitoral bod A reduction glansplasty is rarely utilized. Technical alternatives that preserve the erectile tissue and are therefore theoretically reversible include disassembly of the clitoral elements, with preservation of the neurovascular tissue with the glans and rotation of each corpora int the labia majora as well as caudal advancement of the clitoris between the labia majora as the opposite of historical clitoral recession. The is not sufficient follow-up on either of these approaches to fully understand the patient experience or functional reversibility. A vulvoplast is carried out by extending the incision for the clitoroplasty on either side of the midline strip of tissue down to the level of the vaginal orif Labioscrotal folds are mobilized and moved posteriorly to flank the vaginal vestibule as labia majora. Redundant clitoral skin is reconfigured to form the clitoral hood and labia minora. There are a variety of means by which vaginoplasty can be accomplished throug use of local tissue flaps, autologous free grafts, and/or use of biologic materials such as small intestinal submucosa (SIS) depending upo the nature of the urogenital sinus.

3.2 46,XY DSD

(see **Table 2**)

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Table 2: 46 XY DSD Testicular Development Disorders and Associations

Product	Genetics	Target organs	Syndrome	Phenotype/Associations
WT1	11p13 Autosomal dominant	Kidney Gonad	Denys-Drash Syndrome Frasier Syndrome	Dysgenetic testes resulting in atypical genital with cryptorchidism Bilateral Wilms tumor Nephrotic syndrome — Early onset renal failure /mesangial sclerosis Streak gonads with high risk of gonadoblastoma Female to atypical (ambiguous) phenotype Renal failure, 2nd decade
SF1	9q33 NR5A1, nuclear receptor gene Autosomal dominant	Adrenal Gonad Hypothalamic-pituitary-gonad axis		Dysgenetic testis Variable atypical phenotype-Adrenal failure
SOX9	17q24 Autosomal dominant	Sertoli/AMH Gonad Chondrocytes	Campomelic dysplasia	Dysgenetic testis or sex reversal External spectrum: Male with UDT to atypical to female Shoulder girdle, spine, pelvic anomalies; bowed legs Cleft palate

3.2.1 Definition

46,XY DSD is a group of conditions, previously known as **Male Pseudohermaphroditism**, which involve a defect in testicular development, androgen production or androgen activity.[16] There are 4 sub-categories in this group of DSD (See the DSD Consensus Statement reference for a complete list of included conditions):[14]

- *Abnormalities in testicular development:* dysgenetic testes (mutations and impaired function of SRY, WT1, SF1, SOX9), testicular agenesis (rare), (Ovotesticular DSD—see Category 4)
- *Defects in androgen production*: StAR protein deficiency (lipoid CAH), 3βhydroxysteroid dehydrogenase 2 deficiency (3β HSD), 17αHydroxylase/17,20 Desmolase deficiency (17αH/17,20D), 17βhydroxysteroid dehydrogenase deficiency type 3 (17βHSD3); LH receptor mutations/Leydig cell hypoplasia, 5-alpha reductase 2 deficiency (5αRD2)
- *Defects in androgen receptor (AR) function*: Androgen Insensitivity Syndrome (AIS), complete (CAIS) and partial (PAIS)[1]
- *Other*: Persistent Müllerian Duct Syndrome (PMDS), vanishing testis syndrome/testicular regression (TR), congenital hypogonadotropic hypogonadism (CHH)

3.2.2 Presentation

The degree of masculinization of the external genitalia, including phallic length, phallic curvature, position of the urogenital sinus/urethral meatus, fusion of the labioscrotal folds and position of the gonads is very diverse under the umbrella term of 46,XY DSD. The phenotype ranges from female-typical externally (CAIS) to male-typical with unilateral UDT (PMDS), with states of partial masculinization and testicular maldescent in between.

3.2.3 Pathophysiology

Genital development ensues after testis determination. Development and maturation of the external genitalia and Wolffian ducts are androgen-dependent, by systemic and paracrine influences, respectively. Testosterone (T) produced by the fetal Leydig cells is responsible for early differentiation to male after 8 weeks and maturation of Wolffian ducts (vas deferens, epididymis, seminal vesicles). Later development of secondary sex characteristics and male habitus is T dependent. Spermatogenesis has multiple early and late T dependent steps. Dihydro-testosterone (DHT) is responsible for completion of fetal male development of the penis, urogenital sinus/urethra, and scrotum by 14 weeks. Subsequent fetal penile growth is partially androgen dependent and partially somatic, as T gradually declines after peaking at 11 weeks gestation.

3.2.4 Evaluation

See **Section 4.2**

With return of the 46,XY karyotype, the diagnosis will be guided by the gonadotropin, T and DHT levels. The timing of the labs must be taken into consideration, due to the bi-phasic neonatal gonadotropin and testosterone surge. An **hCG stimulation test** may be necessa to quantify testicular functional potential if the typical natural testosterone peaks are missed or do not occur (central defect, LH receptor defect, testicular regression) or to further characterize the **T/DHT ratio** for diagnosis of 5αRD2 (>30:1, although condition may still be present even with lower T/DHT).

A pelvic ultrasound can be useful to look for Müllerian structures (prominent in newborn due to maternal hormonal influence) and gonads Failure to identify testes does not exclude their presence. An **anti-Müllerian Hormone (AMH, also known as Müllerian inhibiting substance) level can provide additional information regarding functional testicular tissue** in select cases. When distinguishing different types of testosterone synthesis or androgen receptor defects, gonadotropin or steroid levels help make the diagnosis (**Table 3**)

Table 3: Hallmark Hormone And Gonadotropin Levels In Evaluation Of 46,XY DSD

46,XY DSD	Elevated steroid	Decreased steroids	LH	Other
StAR		All in adrenal cascade. Not responsive to ACTH or hCG stimulation		Elevated ACTH and renin
3βHSD	Pregnenolone 17OHpregnenolone DHEA/ DHEAS	(T) (Cortisol) Expected products are paradoxically increased		ACTH
17αH/17,20D	Pregnenolone Progesterone Deoxycorticosterone Corticosterone	Cortisol (T)	Elevated	ACTH
17βHSD3	Androstenedione	(T)	Elevated	
Leydig cell hypoplasia	No elevated precursor	T	Elevated	
5αRD2	(T)	DHT		
CAIS	T		Elevated	

3.2.5 Management

Currently, most individuals with a 46,XY karyotype, when identified in the newborn period and exposed prenatally to androgen, are **rais as male**, presuming agreement of the multispecialty team and parents after review of available data. A course of androgen to stimulate phallic growth may assist with final decision but is not required. Surgical therapy, such as orchiopexy or hypospadias repair (see **Hypospadias**), follows only after there is confidence with assignment and agreement of team and parents. **PAIS** presents the greatest heterogeneity and the biggest challenge in this regard; psychosexual concerns may be more common patients with the highest degree c genital atypia (most ambiguous). For conditions other than **CAIS**, some degree of masculinization will occur with puberty if the gonads remain in place. **Timing of gonadectomy in CAIS** is an area of controversy and evolution in practice. Gonadectomy has traditionally occurred at the time of diagnosis or after pubertal development. Given the low risk of malignancy and some patients reporting dissatisfaction with synthetic estrogens, some advocate leaving the gonads in place for ongoing natural aromatization of T to estrogen. I after thorough counseling the patient and family elect to retain the gonads, a lifelong plan for ultrasound surveillance for malignancy sho be discussed but there is no evidence that ultrasound surveillance improved outcomes.

There are kindreds of individuals with **5αRD2** in the Dominican Republic, Papua New Guinea, and other areas. The condition is well accepted, as the children live as females until puberty, when masculinization occurs and gender identity changes to male. There is some variability that may be explained by the enzymatic defect or societal factors.[9,15]

In **PMDS**, management involves orchiopexy. Previously, there was concern for cyclic hematuria or uterine malignancy if the uterus was l in place. There is no clear support for this concern, and the uterus should be preserved, splitting if necessary, to avoid damage to the va deferens and gonadal vasculature during orchiopexy.

For 46,XY DSD in general, enrollment with a multidisciplinary DSD team is encouraged for longitudinal access to counseling and to allow better characterization of long-term medical, psychosexual and surgical outcomes. Pubertal endocrinologic management is dictated by t degree of spontaneous gonadal function and current gender identity. If sex hormone supplementation is required for puberty or seconda sex characteristics, the patient's desire for rapid physical changes must be balanced with risk of height limitations due to premature fusio of the growth plates.

3.2.6 Malignancy Risk/Fertility Potential

With **Denys-Drash (WT1) and Frasier syndrome**, the risk of malignancy is high (40%) and gonadectomy is recommended for most cases. Gonadectomy is also recommended for **StAR deficiency. 17βHSD deficiency** has moderate risk and monitoring is recommend if diagnosed in childhood, but diagnosis may not occur until puberty. The risk of malignancy in **5αRD2 deficiency** is thought to be minim and there is no specific recommendation for biopsy or gonadectomy. Potential for germ cell tumors is high (50%) in **PAIS with non-scrotal testes** and moderate (unknown %) for **PAIS with scrotal testes**. Gonadectomy is recommended for the non-palpable test and biopsy at puberty is recommended for scrotal testes. The potential for malignancy in CAIS is low (~2%) at time of diagnosis in adolescence but the risk increases with time after puberty. Traditionally the gonads were removed at the time of diagnosis, but many experts now agree that there is minimal increased risk of retaining the gonads until after puberty[21,24] even into early adulthood.[25] If the gona are left in place long-term in CAIS patients, a lifelong monitoring protocol (along with its diagnostic limitations) should be considered.

Fertility depends upon maturation of germ cells relative to the androgen environment. Fertility will not be possible for many patients with 46,XY DSD due to abnormal T exposure or response. Fertility is possible in **5αRD2** but assistive reproductive techniques are likely needed. Fertility is unlikely from **dysgenetic** testes or **CAIS** due to absence of germ cells by puberty. Fertility in **PAIS** is possible, depending upon severity of insensitivity and retention of scrotal testes. Fertility in **PMDS** may be diminished. Experimental pediatric fert preservation techniques (gonadal tissue cryopreservation) have recently been applied to pediatric patients undergoing clinically-indicate gonadectomy for tumor risk.[26] Most patients with DSD who have had their gonadal tissue preserved will be reliant on future developments in assisted reproductive technologies if they have desire for biological parenthood in the future.

3.3 Gonadal Dysgenesis

3.3.1 Definition

GD disorders comprise a wide spectrum of anomalies ranging from complete absence of gonadal development to early gonadal failure. **Complete GD (CGD)** includes failed gonadal development, and can be found in patients with both 46,XX and 46,XY chromosomes, and occur due to abnormalities of sex or autosomal chromosomes. Turner syndrome refers to individuals usually with karyotype 45,X or 45,X/46,XX with gonadal dysgenesis and other typical phenotypic findings. **Partial gonadal dysgenesis (PGD)** refers to disorders with varying degrees of bilateral testicular dysgenesis and typically the karyotype is 46,XY. **Mixed gonadal dysgenesis (MGD)** refers to disorders where there is a unilateral streak gonad and contralateral dysgenetic testis and the karyotype is typically 45,X/46,XY.

3.3.2 XX Complete Gonadal Dysgenesis: Presentation and Pathophysiology

46,XX CGD is characterized by normal stature, normal external and internal female genitalia and Mullerian structures, a complete lack o

pubertal development, and bilateral streak gonads. Typically these patients present with amenorrhea and lack of secondary sex characteristics. **46,XX CGD** is a heterogenous condition occurring sporadically, or when familial, as an autosomal recessive trait.

3.3.3 Turner syndrome: Presentation and Pathophysiology

Turner syndrome may be diagnosed by prenatal karyotype, typical Turner physical stigmata (short stature, shield chest, wide nipples, webbed neck), or amenorrhea with a complete lack of pubertal development. Karyotype can be 45,X or 45,X/46,XX. Some amount of 45,X/46,XX mosaicism may be present in a majority of Turner syndrome patients. In addition, about 10% of Turner syndrome patients w have a mosaic karyotype of 45,X/46,XY with a small amount of the 46,XY cell line. **Presence of the Y chromosome in Mosaic Turner syndrome confers the increased risk of gonadal tumors.** Therefore, in addition to karyotype which may miss the small amount of 46,XY cell line, a FISH or PCR analysis is recommended to identify Turner syndrome patients with Y chromosome material.[27]

In 45,X Turner syndrome, the gonads develop into ovaries but then degenerate into streak gonads with ovarian like stroma and little to n germ cells. Although bilateral streak gonads are the rule, primary follicles have been described in the genital ridges of some individuals, correlating with the rare occurrence of menarche. Conceptions have been documented despite karyotyping revealing only 45,X cell lines 45,X may be due to non-disjunction or chromosome loss during gametogenesis in either parent resulting in a sperm or ovum without a sex chromosome.

3.3.4 XY Complete Gonadal Dysgenesis (Swyer syndrome): Presentation and Pathophysiology

46,XY CGD (**XY sex reversal or Swyer syndrome**) occurs secondary to the absence of testes development despite a Y chromosome. There is no testosterone or AMH production from the bilateral streak gonads. Therefore, external genitalia appear female-typical and the are normal internal Müllerian structures. Patients display complete lack of pubertal development and amenorrhea at the time of expected puberty. Heterogenous causes for this condition can result from deletions of the short arm of the Y chromosome, SRY gene mutations, alterations in autosomal genes, or duplications of the DSS locus on the X chromosome.

3.3.5 46,XY Partial Gonadal Dysgenesis: Presentation and Pathophysiology

PGD typically refers to patients with a 46,XY karyotype and varying degrees of bilateral testicular dysgenesis. There are varying degrees of genital atypia and undescended testes (see **AUA Guideline: Cryptorchidism** and see AUA **Care Foundation: Undescended Testicles Patient Guide**). The internal anatomy can vary from male-typical internal anatomy to presence of rudimentary Müllerian structures. PGD is a result of impaired testicular determination in the presence of *SRY*. Mutations in the pseudoautosomal region of the chromosome upstream of the SRY gene have been identified in PGD. Many of the previously discussed mutations associated with CGD have also been reported in PGD, although the etiology of PGD remains unknown in most cases. Patients reared as males may undergo spontaneous puberty if they have at least one testis able to be brought to scrotal location but typically are infertile and testosterone supplementation may be needed.

3.3.6 45,X/46,XY Mixed Gonadal Dysgenesis: Presentation and Pathophysiology

MGD typically refers to patients with a karyotype of 45,X/46,XY with a unilateral intra-abdominal streak gonad and a contralateral dysgenetic testis. Karyotype variants such as 45,X/47,XYY can occur as well. The intra-abdominal streak gonad typically has associated ipsilateral rudimentary Müllerian structures associated with it due to lack of local AMH activity. The dysgenetic testis can be fully descended or undescended. A variable degree of genital atypia is present. Patients are typically infertile and in patients reared as males the dysgenetic testis may fail in adulthood requiring testosterone supplementation. In addition, patients often have stigmata of Turner's syndrome due to the 45,X cell line and often need growth hormone supplementation. **Patients with MGD should have the same medi screening tests (e.g. hearing, vision, renal, cardiac) as patients with Turner Syndrome. In contrast to patients presenting with genital atypia and mosaicism, 95% of prenatally detected patients with an 45,X/46,XY karyotype have a male-typical phenotype** However, subfertility and/or gonadal failure may present in adulthood in these cases.

3.3.7 Evaluations

Laboratory and radiologic evaluation occurs as outlined in **Section 4.2**.

3.3.8 Management of Gonads in Gonadal Dysgenesis

Many of the management questions for urologists in GD revolve around whether to proceed with gonadectomy and the timing of gonadectomy. **There is an increased risk for gonadoblastoma and dysgerminoma in dysgenetic gonads when Y chromosome material is present.**Gonadoblastoma is a slow growing neoplasm that may undergo late degeneration to dysgerminoma. The timeline fo development of gonadoblastoma and for the more concerning dysgerminoma is not uniform. The risk of gonadoblastoma and dysgerminoma appears to be correlated to degree of GD which is correlated to location of gonad/testis. For example, in 46,XY complete GD the risk of gonadoblastoma or dysgerminoma in the intra-abdominal dysgenetic streak gonads may be up to 35% in adolescence. Conversely, in patients with 45,X/46,XY MGD who have one dysgenetic testis in a normal scrotal position, the risk of gonadoblastoma m

be very low in the scrotal dysgenetic testis.[28]

If a dysgenetic testis is in a normal scrotal position and a male sex of rearing is chosen, it should be left in place (PGD or MGD) with plan for monitoring and possible biopsy after puberty. If a dysgenetic testis is in the inguinal position or lower (PGD or MGD) but not in a normal scrotal position and male rearing chosen, an orchiopexy with biopsy at time of orchiopexy is recommended with plans for monitoring and possible biopsy after puberty. If a dysgenetic testis is undescended and cannot be brought to a normal scrotal position, consideration to gonadectomy should be given, even with male sex of rearing.[28] Historically gonadectomy was performed for patients with fema sex of rearing, but as indicated in prior sections, this may be deferred. If the gonad is in the abdomen and appears to be a streak gonad, bilateral for XY CGD (Swyer syndrome) or unilateral for 45,X/46,XY MGD, then the treatment options include laparoscopic or open removal of the streak gonad.

When a purely female-typical anatomy exists and the presence of Y chromosome material has been ruled out by FISH/PCR, such as in Turner syndrome, no gonadectomy may be necessary (e.g., 45,X, 45,X/46,XX, or 46,XX). These girls often have complete lack of puber development at the time of expected puberty, but some degree of female-typical pubertal development may be seen in up to 20-25%, so preservation of gonads may have some value. Although rare cases of spontaneous pregnancy have been reported, infertility usually occurs. Pregnancy may be possible using donor eggs and assisted reproductive techniques. In females with Turner syndrome that have mosaic karyotype with presence of Y chromosome material (45,X/46,XY), discussion regarding removal of the bilateral gonads is require The current standard of care in these patients is bilateral gonadectomy, but this would remove the small potential for spontaneous puber development mentioned above. If after extensive counseling the family and patient elect to retain the gonads until after any possible spontaneous puberty, a surveillance program and associated risks will need to be outlined.

3.4 Ovotesticular DSD

3.4.1 Definition

Ovotesticular DSD (OT-DSD), formerly known as **true hermaphroditism**, is a condition in which the affected individual is **born with bo ovarian and testicular tissue.**[20]

3.4.2 Presentation

Most affected individuals present as newborns with an atpyical appearance of the external genitalia, with a range of clitoro-phallic size, minimal labioscrotal fusion, and palpability/ descent of zero to one gonad. Ovotestis is the most common gonad. **The most common combination is "unilateral" with either a testis or ovary on one side and an ovotestis on the other**. Ovary/testis and ovotestis/ovotestis also occur. Upon exploration, a uterus is often present. The development of the internal genital ducts is determined b extent of paracrine function of the ipsilateral gonad (testis component). Later presentations with female-typical external phenotype, isola penile hypospadias, or increasing awareness of genital difference during puberty also occur.

3.4.3 Pathophysiology

The most common karyotype for OT-DSD is 46,XX (60%, higher in Southern Africa), surprising given the concept that all of these individuals have testicular tissue and would be expected to have Y chromosome material. Furthermore, many of these individuals with a 46,XX karyotype are SRY negative (no translocation of SRY to X chromosome). The testis-determining factor in the absence of Y materi is not well understood. 46,XX/46,XY mosaicism or chimerism and less commonly 46,XY occur as well. The degree of atypia (ambiguity) the external genitalia is influenced by the gonadal function. The same applies to the internal genitalia but the influence is due to the ipsilateral gonad (paracrine).

OT-DSD is uncommon worldwide, estimated 3-10% of all DSD, but in Southern Africa it represents approximately 50% of DSD. There is similarity in terms of karyotype and phenotype in some 46,XX males and 46,XX OT-DSD; both have occurred in the same family.

3.4.4 Evaluation

Testosterone, either basal during "mini-puberty" of infancy or by hCG stimulation, will be important in making a diagnosis and for sex assignment. Pelvic ultrasound is useful to identify a uterus and possibly gonads. When OT-DSD is considered, laparoscopic examinatio of the pelvic organs and gonads is needed.

Presence of a uterus supports the diagnosis. Confirmation and decision-making regarding gonad management requires biopsy via laparoscopic or open technique, depending upon anatomy. The biopsy should be longitudinal to reliably sample the entire gonad; the testicular and ovarian moieties can be clearly polar or may be admixed throughout an atypical globular gonad. Endoscopic assessment the urogenital sinus is performed under the same anesthetic.

3.4.5 Management

Historically, there is no typical sex assignment for these infants. Sex of rearing is now assigned by agreement of the multispecialty team and parents after review of all laboratory information, an understanding of prenatal and future potential endocrinologic milieu,

consideration of fertility potential, and structure and function of the genitalia. Female assignment may be considered due to the anatomic and physiologic potential for fertility, although the impact of prenatal exposure to androgen is the confounding element of gender identity The testicular tissue does not have normal functional potential over the long run (after one year per Southern African experience)[29] and hormo replacement is likely needed if a male-typical puberty is desired. A large South American cohort with average follow-up of 25 years favor male assignment.[28] The degree of masculinization of the infant, suitability for functional reconstruction, and the basal or hCG-stimulated testosterone level may also guide the decision for sex assignment. The need for hormone replacement or supplementation at puberty is guided by the endocrinologic capacity and gender identity at that time.

3.4.6 Malignancy Risk/Fertility Potential

Risk of malignancy is low, even in setting of Y chromosome, as ovarian tissue is well-developed and testicular germ cells become increasingly deficient over time. Fertility via the ovarian tissue is possible if a well-developed uterus is present. Testicular tissue is abnormal and spontaneous fertility has not been reported in males. Separation of ovarian and testicular tissue may not be possible, how

4. Examination of the Newborn with Potential DSD

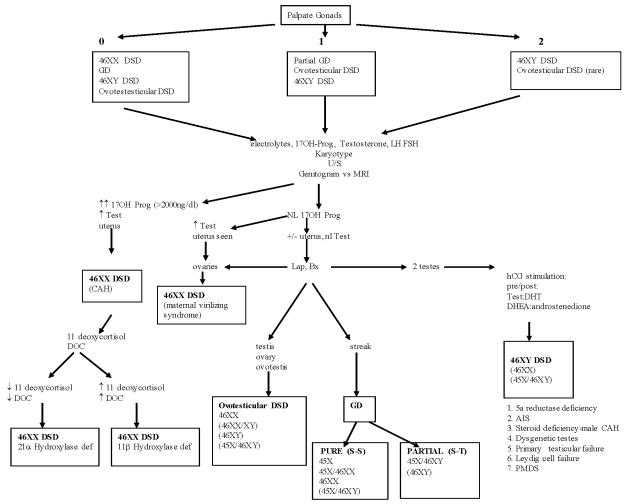

Figure 2: DSD Evaluation Algorithm

Figure 2 shows a suggested algorithm for working through potential diagnoses outlined above when a newborn with a possible DSD presents for medical attention.

4.1 Pertinent History and Examination

4.1.1 History

It is important to elicit the **level of prematurity**, and **maternal ingestion of or exposure to exogenous hormones**. Family history includes any **urologic abnormalities**, **neonatal deaths**, **precocious puberty**, **infertility**, or **consanguinity**. Note **abnormal masculinization** or **Cushingoid appearance of the child's mother**. Document fetal testing such as karyotype testing via methods including cell-free DNA or amniocentesis, and sonogram determination of fetal genitalia.[7,8]

Prenatally established expectations by the family in terms of sex/gender of the baby may make the neonatal period more difficult and emphasize the role of the health care team in providing accurate information and support.

4.1.2 Physical Examination

It is important to use gender neutral anatomical terms when charting and speaking with the family and all other team members. Rather than uninformed pronouns, consider *your baby* or *the baby*. **Offer congratulations and support** and acknowledge what is known/not y known regarding the baby. Inform the family how and when new information will be shared with them.

Note any dysmorphic features (short broad neck or widely spaced nipples), development, rugation and pigmentation of labioscrotal folds clitorophallic width and stretched length, position of the urethral meatus, presence and degree of clitorophallic curvature (chordee), and the number of orifices: three (urethra, vagina, and anus) versus two (urethra, anus). Document the palpability of gonads (**Figure 2**).

If no gonads are palpable, any DSD diagnosis is possible (**46,XX CAH most common**). If one gonad is palpable, **Complete gonadal dysgenesis** (CGD) and 46,XX DSD are ruled out (exception: ovotesticular DSD can have a 46,XX karyotype). **Partial gonadal dysgenesis (PGD), Mixed gonadal dysgenesis** (MGD), ovotesticular DSD, and 46,XY DSD remain possible. If two gonads are palpab 46,XY DSD and rarely ovotesticular DSD are the most likely. Examples of how to describe the newborn exam are in **Figure 3**.

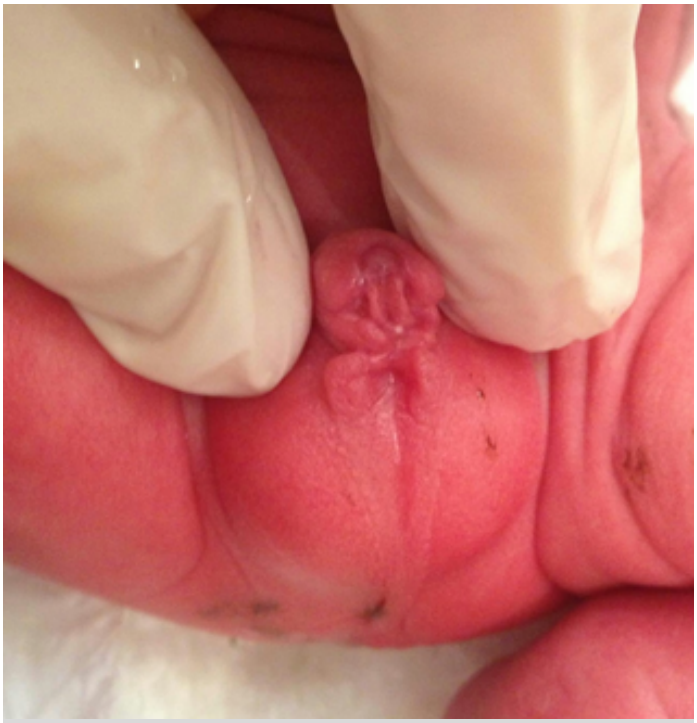

Figure 3a: Infant A: 1.5 cm hooded clitorophallic structure with single orifice at base. Fusion of non-rugated, non-pigmented labioscrotal folds with intact but splayed raphe. Gonads palpated near pubic tubercle. Normally positioned and patent anus.

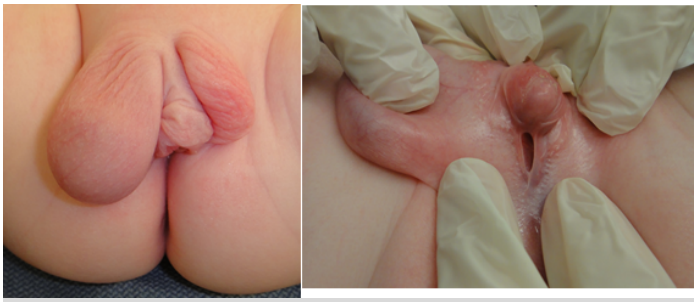

Figure 3b: Infant B: >2 cm hooded clitorophallic structure with ventral curvature and short mucosal plate between generous perineal orifice and tip of glans. Labioscrotal folds rugated and anteriorly positioned with a palpable gonad on the right. No posterior fusion of labioscrotal folds. Normal anus.

4.2 Evaluation

Laboratory evaluation includes **karyotype, serum electrolytes, 17OH progesterone, T, LH, and FSH levels**. Based upon the initial laboratory data, the workup can be individualized to reach the diagnosis. For example, if the 17OH-progesterone level is elevated, 11-deoxycortisol and DOC levels differentiate 21α-hydroxylase deficiency from 11β-hydroxylase deficiency (thus distinguishing the two most common forms of CAH). If the 17OH-progesterone level is normal, a 46,XY DSD is more likely. A T:DHT ratio and/or androgen precursors before and after hCG stimulation may help elucidate the 46,XY DSD etiology. The hCG stimulation test is not needed from 60-90 days of life when there is a natural gonadotropin surge and resultant increase in T level. Thus, an hCG stimulation test is not needed in all cases of 46,XY DSD, as this mini puberty of infancy can be used to capture the needed hormonal information for many patients. A failure to respond to hCG in combination with elevated LH and FSH levels or low level of AMH with elevated gonadotropins is indicative of functional anorchia.

More advanced investigations may be applied selectively based on patient examination and initial laboratory results. Advanced genetic testing options are shown in **Table 4**. Along with the results of initial investigations, the decision to pursue advanced genetic testing depends on other factors including parental preference to have an explanation for a genital difference, and (unfortunately) cost.

Ultrasound can identify Müllerian structures or inguinal gonads. Retrograde instillation of contrast for **genitogram** informs the urogenit sinus anatomy, including the confluence of the urethra and the vagina and a cervical impression. Endoscopy provides similar information anesthesia is otherwise needed. **MRI with gadolinium** delineates the pelvic anatomy and presence of gonads, but is more costly and **typically requires general anesthesia**. Infants with DSD, other than CAH, sometimes require an open or laparoscopic exploration with bilateral deep longitudinal gonadal biopsies for histologic evaluation.

Table 4. Adjunctive Genetic Testing Options

Genetic Test Name	Indication
FISH for SRY	Evaluation of individuals with genitalia/karyotype discrepancy (e.g., 45,XX with masculinized genitalia)
Single Gene Testing	To confirm a diagnosis highly suspected based on history and clinical findings
DSD Slice (Targeted DSD gene panel)	Evaluate for specific gene mutations known to be associated with DSD
Microarray	Rapidly scan for multiple mutations (including possibly new candidate genes) where diagnosis is unclear, and/or multiple congenital anomalies present
Whole Exome Sequencing	Indications similar to microarray; broader analysis may yield a diagnosis when other testing is not diagnostic
Whole Genome Sequencing	Indications similar to microarray; broad enough to replace whole exome sequencing, targeted gene panels and microarray, but is new and not universally available

4.3 Multidisciplinary Team

Evaluation immediately after birth and further management of a patient with suspected DSD should always involve a multidisciplinary team approach. The DSD team includes the **pediatric urologist, endocrinologist, psychologist, and the child's parents. Some centers also involve pediatric surgery and/or pediatric gynecology. A geneticist and/or genetic counselor is often involved as well when the diagnosis is not immediately clear or if genetic testing beyond a karyotype is being considered. For many patien** can be helpful to have visits with multiple specialists together in the same clinic to provide a coordinated approach.

4.4 Sex Assignment and Gender Identity

Much current research is aimed at understanding the influence of androgens on the fetal and newborn brain and its relationship to gende identity. Diagnosis and management of each child is individualized, and not template-driven.

Since the newborn is not able to contribute to early decision making, sex of rearing for a newborn is mutually decided upon by the paren and the medical team based upon best available information about the patient's diagnosis and likely future gender identity. This decision is made with the understanding that there is much yet to learn and that this child may grow up to declare a gender identity inconsistent with the binary male or female assignment rendered in infancy.

In general, newborns with 46,XX CAH have typically developed ovaries and uterus and are most commonly raised female. Ther are case series of individuals with late diagnosis of 46,XX CAH raised male with stable male gender identity and committed partnership with females[30] Masculine gender role behaviors, homosexuality and bisexuality may be more common in women with 46,XX CAH than th general population, but gender dysphoria and seeking a legal change in gender is less frequent (9% in one large experience). There is n clear predictive feature of gender identity CAH. Gender dysphoria among those raised male is more common. The psychological experience of gender dysphoria among individuals with CAH appears to be distinct from that in transgender individuals who do not have known DSD diagnosis.[31]

In individuals with complete androgen insensitivity syndrome (CAIS) diagnosed based upon prenatal or neonatal information, female sex assignment is recommended Most individuals with CAIS will not be diagnosed in the neonatal period and female will have been presumed based upon phenotype.

Partial androgen insensitivity syndrome **(PAIS) involves a spectrum of insensitivity and corresponding true androgen "exposure" and phenotype, and support of male sex of rearing is typically prudent.**[1] Male rearing is also appropriate when a deficit in 5-alpha-reductase is identified, as further masculinization occurs during puberty. These latter diagnoses, along with ovotesticular DSD a 45,X/46,XY gonadal dysgenesis, present a greater challenge in terms of confidence with assignment of sex of rearing.

Decisions regarding surgical intervention, particularly irreversible procedures, become even more complicated and sensitive as future gender identity and preferences become less intuitive. Traditionally, sex assignment was based upon natural fertility potential and ability to surgically create a functional urinary and genital tract. Gonadal tissue incongruous with sex assignment was removed. Assigning sex and presumptive gender had an early surgical component. However, with increasing recognition of the concept of non-binary gender identity and from voices of the affected community regarding self-determination and medical necessity, surgical decision-making is evolving. Intentional preservation of future options (gonadal tissue, uterus) is increasingly recommended in the medical community.[23,24] Options clitoroplasty that preserve all erectile tissue are also being explored.[25] Gonadal hormone production after the 'mini-puberty' of infancy is negligible, and the risk of germ cell tumor prior to puberty is very low, so deferring a decision for gonadectomy until the child is old enoug to verbalize their preference is an option for some patients. If a decision for male sex of rearing is reached, orchiopexy is recommended, possible, to position the testis for better future functional potential. Active observation (by ultrasound) of nonpalpable dysgenetic gonads recommended, though recommended screening intervals have yet to be established. For streak gonads, where likelihood of function and fertility from that gonad is very low, the timing for gonadectomy is based upon discussion with the family regarding tumor risk tolerance balanced against desire to observe for function.

5. Presentation of DSD after the Newborn Period

Several conditions included in the new nomenclature first come to clinical attention in childhood or at the time of puberty. Similar to evaluation of newborns, first line evaluation includes chromosomal analysis to determine karyotype, gonadotropin and sex steroid levels and inguinal and abdominal US. Four clinical scenarios may arise:

5.1 Primary Amenorrhea

1. Complete lack of pubertal development with hypergonadotropic hypogonadism: 46,XY GD (Swyer syndrome), 45,X and 46,XX GD complete Leydig cell hypoplasia.
2. Normal or partial pubertal development: CAIS, (PAIS), (45,X GD, 45,X/46,XY Turner mosaicism)
3. Masculinization evident with puberty: 17βHSD3, 5αRD2, partial Leydig cell hypoplasia, gonadal dysgenesis variants with abdomina dysgenetic testis, non-classic CAH, (PAIS)

5.2 Incidental Findings upon Emergent Abdominal Exploration/Laparoscopy or CT Scan

Absence of a uterus +/- finding of solitary kidney may suggest **MRKH** or **Müllerian agenesis**. CAIS is also a potential diagnosis but is n associated with renal anomaly. The two are distinguished by visual characteristics of the abdominal gonads (ovaries vs testes), and karyotype (46,XX vs 46,XY). (See **Figure 4** and **Figure 5**)

An atypical gonad appearance for external phenotype could suggest GD or CAIS. T, estradiol and gonadotropin levels may provide supporting information if presentation occurs around the age of puberty.

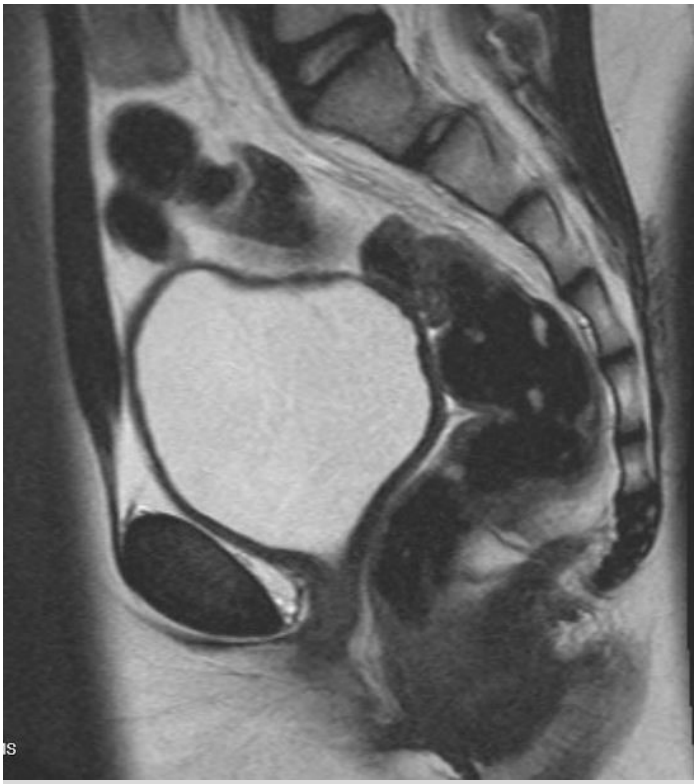

Figure 4: Müllerian agenesis. Note the absence of uterus and vagina between the bladder and rectum in the setting of primary amenorrhea by MRI T2 sequence. Unilateral renal agenesis is common but not demonstrated in this series.

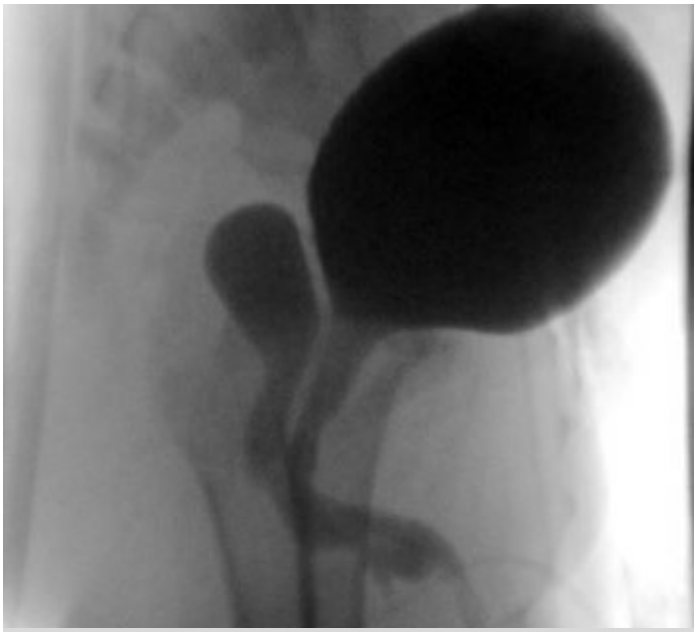

Figure 5: Müllerian remnant in DSD. Although utricles project from the verumontanum, this remnant inserted just inside the

perineal urethral orifice and has proportions similar to a vagina. There was no uterus. After hypospadias repair the child developed urinary tract infections and the remnant was excised via anterior sagittal transrectal approach.

5.3 Inguinal Hernia in Female Child

While this does not commonly herald a DSD, inguinal hernia in a child with female-typical external genitalia does warrant investigation. CAIS, 5αRD2, PAIS or 17βHSD3 may present with childhood hernia. Inguinal exploration without a purposeful search may not identify th gonad. When a young girl presents for inguinal hernia repair, vaginoscopy confirming presence of a cervix rules out these conditions. Preoperative karyotype is another approach to eliminate possibility of DSD.

5.4 Masculinization of Female in Childhood

'Non-classic' CAH presents as early childhood or prepubertal development of pubic hair +/- clitoral enlargement. Masculinizing adrenocortical carcinoma is another uncommon possibility.

5.5 Abnormal Karyotype Detected on Genetic Evaluation for Another Condition

Children with conditions including short stature, developmental delay, or neuropsychiatric concerns can be diagnosed with sex chromosome abnormalities such as 45X, 46XY Turner Mosaicism.

6. Psychosocial Aspects of DSD

A critical part of the modern DSD care paradigm is attention to the psychological well-being of individuals and their parents. Inclusion of mental health support and resources in the care of the family from the time of diagnosis onward is recommended. Although an infant is t young to directly benefit from work with mental health professionals, they likely benefit indirectly through support and information provide to the family by the whole care team. There is ongoing assessment of the varying degrees of distress family members experience relate to the child's diagnosis and its future impact.[32] Parents report the need for knowledgeable resources and support.[33] Mothers and fathers ma manifest distress differently, and based upon the spectrum of DSD and the spectrum of parents, there will be variation in individual experiences as well.[34,35,36] Their experience may in part shape their parenting style,[37,38] which in turn may impact the child's psychosocial development. Forming a relationship with the family normalizes a long- term relationship with the patient as they pass through various lif stages and potential challenges together over the years. The mental health professional can therefore be extremely helpful with finding words for age-appropriate disclosure of history and decisions made on behalf of the child. These team members can also help support children and their families through future decisions about medical and surgical treatments for DSD.

7. Update on Recent Political Events, Recommended Practice Patterns and Controversies:

The United Nations has brought international focus upon genital surgery in children. The Human Rights Watch has partnered with multip organizations to end medically unnecessary genital surgery in young children. Definitions of medical necessity may not necessarily align across these groups, medical providers, parents and affected individuals. Litigation against individual practitioners has been pursued in isolated cases in the past decade. Legislation has been explored in multiple states within the past few years, but no official legislation regarding genital surgery has passed. In August 2018 California passed resolution SCR-110 promoting the right of affected individuals t participate in decisions about surgical alterations of their bodies. The verbiage in that resolution could eventually have implications for procedures unrelated to DSD, such as circumcision and repair of isolated hypospadias or cryptorchidism. In 2021, New York City passe legislation requiring a "a public information and outreach campaign regarding the provision of medically unnecessary treatments and interventions performed on individuals born with intersex traits or variations in sex characteristics".[39] At the time of this curriculum update, forma legislation restricting surgical options for patients with DSD has not passed in the United States, though legislation has passed in other countries including Germany[40] and Greece.[41] Testimony of affected individuals and their loved ones, whether in support or opposition to surgery, is understandably difficult but impactful during legislative hearings. Engagement by practitioners in various disciplines who frequently care for individuals living with DSD/intersex is also important.

A call to have various major medical organizations take a stand on the issue has been answered and various organizations have generated position statements.[42,43,44] Although the importance of additional data to shape guidelines is acknowledged, to date none have denounced parents' rights to make well informed decisions on behalf of their child. It is our responsibility to provide balanced information for that decision process. The American Medical Association continues to support shared and informed decision making on behalf of the child, while supporting self-determination and participation in decisions when possible.[45]

Among affected individuals and parents whose experiences were highlighted in the Human Rights Watch and in various news pieces or documentaries, there is a common theme. There appears to be dissatisfaction with the information provided to these parents and affecte individuals about their conditions and about procedures performed or proposed. Some of these personal accounts were of encounters

from decades ago and some appear to be relatively recent. In some cases, a diagnosis and history are shared, and in some cases, the clinical details are missing but personal scars are shared. Each personal story has value and we need to hear more to continue to shape the care paradigm. We have some information from individuals who have shared, but statistically speaking, there would be many individuals who are not sharing their experience. The reason for their silence is speculative. Aside from enrolling research participants to understand all experiences (with and without surgery, longitudinal multidisciplinary support, patients with gender dysphoria), a fundamer issue with DSD/Intersex outcomes research is the pooling of various DSD/intersex diagnoses for research and educational presentations A call for research limited to individual diagnoses has been made. Clearly discerning the diagnosis of participants is one anticipated barrier.

A cornerstone of the modern paradigm is to have care delivered by a multidisciplinary team. The team should provide parents of affected infants with as much information about the condition as available. They should be counseled about all management options regarding assigning sex of rearing and its complexity for future gender declaration, medical management, and surgical management from all angle including non-intervention. Likewise, the team should work with families longitudinally to provide ongoing support and information and to reveal the diagnosis and decisions to the affected individual in an age-appropriate fashion. Patient- and family-centered care, with goals providing detailed and balanced information and promoting openness rather than secrecy, is the desired approach. The goal is development of happy, healthy children and adults through the decisions that are reached. Very clearly, the current model does not call f one physician to determine the appropriate course of action; to suggest otherwise is potentially problematic for the patient, family, surgeo and team. Decisions are made jointly by the parents (and patient when appropriate) and the multidisciplinary team.

Certainly, some teams may be more facile with this care delivery model than others, and some parents may be more receptive to this participatory style of care than others. Many babies will be born in hospitals without geographic access to a team. Congratulations on the birth of their baby and an introduction to differences in sex development is an excellent start. Consultation with a multidisciplinary team within the first couple of weeks, even if rendered remotely, is important to provide families the early information and support that they ne Currently parents are legally able to make surgical decisions on behalf of their children. It is our obligation to provide them with the most current information and resources to allow them to make informed decisions for their child. If openness and subscription to long-term car continue to be encouraged, then the quality and reliability of our long-term outcomes data (both with and without early surgical intervention) will improve. It is only through good communication and high-quality data collection that we can modify the care paradigm a answer today's outstanding questions.

8. Acknowledgments

The authors gratefully acknowledge Dr. Tom Kolon for his contributions to this chapter and to the field over the years.

9. Abbreviations

DSD- Disorders of Sex Development or Difference of Sex Development
CAH- congenital adrenal hyperplasia
GD- gonadal dysgenesis
CGD- complete gonadal dysgenesis
PGD- partial gonadal dysgenesis
CAIS- complete androgen insensitivity syndrome
PAIS- partial androgen insensitivity syndrome
T- testosterone
DHT- dihydrotestosterone
LH- luteinizing hormone
FSH- follicle stimulating hormone
HSD- hydroxysteroid dehydrogenase
AMH- anti-Müllerian hormone
DOC-11 -deoxycorticosterone
SRY- sex-determining region Y
WT1- Wilms tumor suppressor gene
SF1- Steroidogenic factor 1
SOX9- SRY-box9
OT-DSD- ovotesticular disorder of sex development
StAR- Steroidogenic acute regulatory protein
3βHSD- 3βhydroxysteroid dehydrogenase 2 deficiency
17αH/17,20D-17αHydroxylase/17,20 Desmolase deficiency
17βHSD3-17βhydroxysteroid dehydrogenase 3 deficiency
5αRD2- 5αreductase type 2 deficiency
AR- androgen receptor

DHEA- dehydroepiandrosterone
PMDS- persistent Müllerian duct syndrome
TR- vanishing testis/testis regression
CHH- congenital hypogonadotropic hypogonadism
MRKH- Mayer-Rokitansky-Küster-Hauser syndrome

Presentations

Disorders of Sexual Differentiation Presentation 1

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