The Neonate with Ambiguous Genitalia

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Education Gaps

1. Clinicians should understand normal sex development and identify physical examination findings that suggest disorders of sex development.
2. Timely targeted evaluation of disorders of sex development can lead to appropriate monitoring and therapies, and earlier sex assignment.

Abstract

Neonates with ambiguous genitalia have various clinical presentations, etiologies, and outcomes, ranging from benign to life-threatening. This review provides a summary of these findings. Some diagnoses may lead to delayed sex assignment. A systematic approach to the evaluation of disorders of sex development can allow for timely treatment and family counseling.

Objectives After completing this article, readers should be able to:

1. Identify infants with a disorder of sex development.
2. Understand the pathophysiology of disorders of sex development.
3. Evaluate an infant with ambiguous genitalia.

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ABBREVIATIONS

AMH	anti-müllerian hormone
CAH	congenital adrenal hyperplasia
DHEA	dehydroepiandrosterone
DSD	disorder of sex development
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
LH	luteinizing hormone
17-OHP	17-hydroxyprogesterone

INTRODUCTION

Ambiguous genitalia in the newborn is an uncommon disorder that is characterized by the appearance of a newborn's genitalia that is different from the expected genitalia based on the newborn's chromosomal sex. Its frequency has been documented to range from 1 in 1,000 to 1 in 5,000 newborns. (1)(2) The finding of ambiguous genitalia can herald a life-threatening underlying issue, and thus, affected neonates must be quickly evaluated and managed. However, this disorder often presents both a challenge for clinicians and a distress to the patients' families, especially if a gender cannot easily be assigned. In a consensus statement published by members of the Lawson Wilkins Pediatric Endocrine Society and the European Society of Pediatric Endocrinology, it has been suggested to use the term "disorder of sex development" (DSD), when addressing this potentially sensitive issue with the patient's family (3); however, this terminology has not been fully accepted outside the medical community. Managing this disorder requires a multidisciplinary team with a long-term

approach in mind; data show that gender dissatisfaction and gender reassignment occurs more frequently in patients with a history of DSD. (4)

NORMAL SEX DEVELOPMENT

Initially, chromosomal sex is determined during fertilization; females normally have 2 X chromosomes, and males have 1 X and 1 Y chromosome. (5) The initial embryonic bipotential gonad develops similarly between male and female fetuses for the first 6 weeks of gestation. The bipotential gonad begins to differentiate around the seventh week of gestation under the direction of transcription factors such as LIM11, WT-1, DAX-1, SRY, and SOX-9, (6) with the default being female. (7)

The Y chromosome contains many genes that are required for male-specific functions; of note is the *SRY* gene, which causes the bipotential gonads to differentiate into testes and produce testosterone via Leydig cells during the eighth week of gestation, with peak production by 10 weeks' gestation. Testicular synthesis of testosterone is controlled by placental or fetal human chorionic gonadotropin (hCG). However, in the second and third trimester this is controlled by fetal serum luteinizing hormone (LH). Follicle-stimulating hormone (FSH) allows proliferation of Sertoli and germ cells during the second trimester. Antimüllerian hormone (AMH) is produced by the Sertoli cells around 7 weeks' gestation, which leads to regression of the müllerian ducts at 8 to 9 weeks' gestation.

The male external and internal genitalia are affected by increased testosterone production, which exerts its effects after being peripherally converted to dihydrotestosterone by 5α-reductase type 2 enzymes. The structures formed are the glans penis, scrotum, and penile shaft, along with the normal migration of the urethral meatus upward to the tip of the glans penis. Internally, the undifferentiated wolffian ducts differentiate into the epididymis, vas deferens, ejaculatory duct, seminal vesicles, and prostate. This process is complete by 12 to 14 weeks of gestation. At birth, the normal external appearance of the male genitalia in term gestation neonates consists of bilateral, descended testicles, fully formed scrotal folds with midline fusion, and an average penile length of 3.5±0.4 cm. (8)

In females, X chromosome–encoded genes, such as *WNT4* and *RSPO1* (R-spondin 1 gene), are not suppressed by *SRY*, and are required for the undifferentiated gonads to become ovaries. Ovarian development does not require 2 X chromosomes. Without increased testosterone or AMH production, the external genitalia form into the clitoris, labia majora and minora, and the urethral groove divides into the urethra and lower third of the vagina. The müllerian ducts persist without AMH and differentiate into the fallopian tubes, uterus, and the upper two-thirds of the vagina. The wolffian duct undergoes regression without the effects of increased androgen. (9) This process is complete by 12 to 14 weeks' gestation. At birth, the normal external appearance of the female genitalia in term gestation neonates consists of bilateral separation of the labial folds, separate urethral and vaginal openings, and the absence of palpable gonads. The fetal ovary lacks hCG- and FSH-binding sites. However, at 8 weeks of gestation, the ovary has aromatase activity and can convert androstenedione or testosterone to estradiol. Most of the estrogen is produced by aromatase.

AMBIGUOUS GENITALIA: BENIGN CAUSES AND ABNORMAL SEX DEVELOPMENT

DSD should be suspected in a neonate who has ambiguous genitalia. This includes bilateral cryptorchidism, bifid scrotum, microphallus, or hypospadias if severe or accompanied by unilateral or bilateral cryptorchidism. Microphallus in the full-term male infant is defined as a stretched penile length less than 2.5 cm, measured from the penopubic junction to the tip of the glans penis of a stretched phallus with complete depression of the suprapubic fat pad. (10) In females, common abnormal findings of DSD may include clitoral hypertrophy, fused labia, or inguinal masses. DSD should also be suspected if the neonate's phenotype is discordant to its known chromosomal sex.

Of note, some cases of an abnormal genital appearance may not be the result of a DSD. In males, anatomic penile abnormalities that likely are not caused by DSD include a concealed penis and paraphimosis. A concealed penis is an anatomically normal penis of normal length that is buried within surrounding prepubic fat tissue or scrotal tissue; in some cases, this finding can be seen after circumcision if adhesions develop secondary to scar tissue formation. This is why it is important to have complete depression of the suprapubic fat pad when examining the penis or assessing penile length. Phimosis, the condition in which the foreskin cannot retract over the glans penis, is normal in prepubertal boys; however, paraphimosis can occur when the foreskin retracts over the glans penis and is unable to return to its original position, causing pain, swelling, and potential ischemia to the structures distal to the entrapped foreskin. In females, hymenal variants may be mistaken for a congenital vaginal abnormality. An imperforate hymen may appear as a bulge at the vaginal introitus, but often is not diagnosed until menarche.

CAUSES OF DSD

Causes of DSD are explained herein and summarized in the Table.

46,XY Neonate with Ambiguous Genitalia

Normal male genital development depends on the differentiation of the testes, the ability of the testes to produce testosterone, the conversion of testosterone to dihydrotestosterone, and the ability of these hormones to enact their effects on different structures in the body.

Gonadal Dysgenesis. Gonadal dysgenesis encompasses different conditions that lead to a partial or complete loss of gonadal development. In newborns with a 46,XY genotype, these conditions are caused by genetic mutations, such as in the *SRY* or *SOX9* genes, but mutations of many other genes that serve as transcription factors for gonadal development have been implicated in the development of bipotential gonads. (11) Leydig cell hypoplasia or aplasia are other types of gonadal dysgenesis, caused by mutations in the *LHCGR* gene, which encodes the LH and hCG receptor, and is necessary for Leydig cell growth and androgen production. Impaired androgen production may lead to improper genital development. If only 1 testis is present, the müllerian ducts on the contralateral side will remain and the circulating testosterone levels will be insufficient for the development of wolffian duct structures.

Deficiency in the Synthesis of Testosterone and Dihydrotestosterone. This arises secondary to defects in the enzymes required to convert cholesterol into testosterone and dihydrotestosterone (Fig 1). Cholesterol is initially transferred into the mitochondria via steroidogenic acute regulatory protein, converted into pregnenolone, and subsequently converted into androstenedione via the actions of 17α-hydroxylase, 17,20-lyase, and 3β-hydroxysteroid dehydrogenase; androstenedione is then converted to testosterone via 17β-hydroxysteroid dehydrogenase. (12) In addition, defects in cytochrome P450 oxidoreductase, which is required for many steps of androgen synthesis, has been implicated in ambiguous genitalia in both males and females. (13) The final step to convert testosterone to dihydrotestosterone, which requires 5α-reductase, is impaired in individuals with 5α-reductase 2 deficiency, secondary to a mutation in *SRD5A2*.

Abnormal Androgen Receptor Activity. This results from mutations of the gene that encodes for the human androgen receptor, which is located on the X chromosome and is known as the *AR* gene. A database of hundreds of mutations of the *AR* gene resulting in varying degrees of undermasculinization is maintained by the Lady Davis Institute for Medical Research at McGill University (http://androgendb.mcgill.ca/). Patients with these mutations often develop streak gonads. These gonads are at high risk of developing tumors. (14)

46,XX Neonate with Ambiguous Genitalia

Female internal and external genitalia will develop normally in the absence of AMH and androgens.

Gonadal Dysgenesis. This is a condition in which the patient will have bilateral streak gonads or hypoplastic ovaries with normal müllerian duct structures and normal female external genitalia. There may be a family history of infertility. These conditions result from an abnormality in a

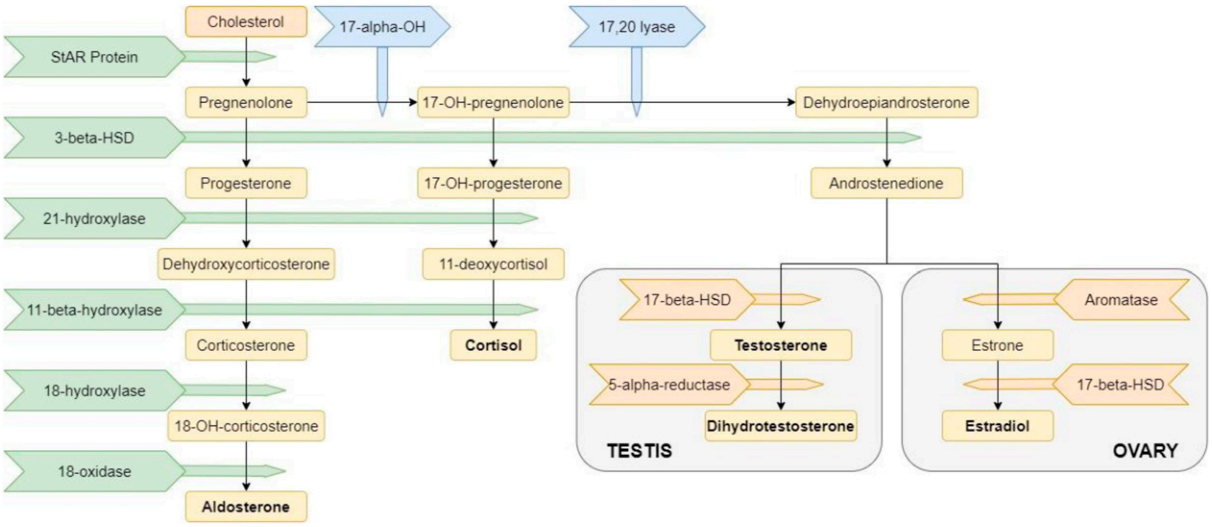

Figure 1. Steroidogenesis pathway. HSD=hydroxysteroid dehydrogenase; StAR=steroidogenic acute regulatory protein; 17-α-OH=17-α-hydroxylase; 17-OH-pregnenolone=17-hydroxypregnenolone; 17-OH-progesterone=17-hydroxyprogesterone; 18-OH-corticosterone=18-hydroxycorticosterone.

gene that regulates germ cell migration, formation of the bipotential gonad, or ovarian differentiation. Possible genes that have been implicated include *FOXL2, WNT4, CTNNB1* (β-catenin), *LHX9, EMX2, Wt1, CBx2, GATA4, Six1/4*, and *NR5A1*. (15)

46,XX with Bilateral Testicles. This condition usually results from an abnormal X to Y translocation occurring during paternal meiosis that allows for a variable amount of Y sequence to be present in the fetus. (16) Most of these patients will have normal male internal and external genitalia, but some may have ambiguous genitalia because of decreased testosterone production. The phenotype is dependent on the amount of testicular tissue. The second X chromosome will lead to absence of spermatogonia, hyalinization of the tubules, and small testes in adults, similar to Klinefelter syndrome.

Androgen Excess. Androgen exposure between 8 and 14 weeks' gestation will lead to male phenotype of the external genitalia such as labialscrotal fusion, regression of the urovaginal septum, phallus-appearing structure. Androgen exposure occurring beyond 12 to 14 weeks' gestation can lead to clitoromegaly. (17)

Congenital Adrenal Hyperplasia. Congenital adrenal hyperplasia (CAH) encompasses multiple autosomal recessive disorders that leads to an abnormality in 1 of the enzymes required for synthesis of cortisol (Fig 1). Each enzyme defect will lead to impaired cortisol production, and lack of negative feedback will lead to excess adrenocorticotrophic hormone secretion. The first 3 enzymes in the pathway are important in gonadal tissue for sex steroid production, and all but 1 are responsible for aldosterone synthesis.

The most common enzymatic errors occur in the 21 and 11 β-hydroxylase enzymes that are found primarily in the adrenal cortex. (18) Deficiencies in either enzyme will lead to excess formation of precursor steroids, which will lead to increased androgens that will induce virilization of the affected female during the first trimester. 21 β-hydroxylase deficiency is the most common cause of CAH (95% of all cases). It is caused by a mutation in *CYP21A2*, (18) and has 2 early-onset forms: the simple virilizing form with partial enzyme deficiency, and the second form that is both virilizing and salt-wasting as a result of complete enzyme deficiency. The third form is a late-onset form that is associated with a mild enzyme deficiency, which does not present until late childhood. The salt-wasting form is caused by an underlying adrenal insufficiency, and affected patients may present in adrenal crisis. Most reported cases of CAH are of the salt-wasting form, with 25% being other types. Virilization can range from clitoromegaly with labial fusion to perineal or penile hypospadias to complete male phenotype. Of note, males can also develop CAH, which usually does not cause excess virilization. Males with the simple virilizing form, if left untreated, can have accelerated growth, early fusion of growth plates, and early adrenarche.

Neonates with the salt-wasting form of CAH are not likely to have an adrenal crisis until 1 to 2 weeks of age; by 1 month or more, more than 75% of affected patients will have developed an episode of adrenal crisis. Clinical symptoms of adrenal insufficiency in a neonate can be nonspecific and include lethargy, vomiting, and weight loss. Abnormal laboratory findings include hyperkalemia, hyponatremia, and metabolic acidosis. If affected patients are not treated, severe symptoms can develop, including dehydration, hypotension, weakness, hypoglycemia, altered mental status, and arrhythmias secondary to hyperkalemia.

Treatment of the simple virilizing form of 21 β-hydroxylase deficiency requires cortisol replacement but does not require stress dosing of steroids. Treatment of the salt-wasting form of 21 β-hydroxylase deficiency requires maintenance glucocorticoid as well as stress dosing of cortisol. Some infants may need mineralocorticoid replacement and salt supplementation. Mineralocorticoid and salt requirements do not change with stress or an increase in body size. Prenatal diagnosis is now available for pregnancies at risk for 21-hydroxylase CAH. The diagnosis can be made with chorionic villus sampling or amniocentesis. Prenatal maternal dexamethasone administration has a high success rate in preventing or minimizing the virilization. (18) However, this practice is controversial because some studies have shown that fetuses exposed to prenatal dexamethasone can have adverse neurocognitive effects (19) whereas other studies did not demonstrate adverse effects. (20)

11β-Hydroxylase Deficiency. This is the second most common form of CAH, causing approximately 8% of cases. This disorder is caused by an autosomal recessive mutation in the *CYP11B1* gene. This deficiency will cause impaired synthesis of cortisol and aldosterone, virilization of the female as a result of increased androgens, and low-renin hypertension because of overproduction of deoxycorticosterone. Affected female neonates are born with virilization ranging from clitoral enlargement to labial fusion, leading to complete male external genitalia. Patients may also have hyperpigmented genitalia. Sodium retention and hypertension can develop. Laboratory testing demonstrates increased levels of serum 11-deoxycortisol. Treatment includes maintenance hydrocortisone that does require stress dosing.

3β-Hydroxysteroid Dehydrogenase Deficiency. This condition leads to poor production of cortisol, mineralocorticoid, and sex hormones, with accumulation of

dehydroepiandrosterone (DHEA). (21) Adrenal insufficiency and salt-wasting can be seen, similar to 21-hydroxylase deficiency. Female infants with this form of CAH may have a degree of virilization because of conversion of DHEA to more potent androgens.

Placental Aromatase Deficiency. This can also lead to increased endogenous androgen exposure to the fetus because of lack of conversion of androgens to estrogen. It is a rare autosomal recessive disorder resulting from a mutation in *CYP19* that can lead to variable female virilization. (22)

Excess Exogenous Androgen. Exogenous androgen levels can become excessive from maternal drug exposure. This may lead to mild virilization that will not progress postnatally. Biochemical studies typically show normal androgens and 17-hydroxyprogesterone (17-OHP) levels. (17)

Dysgenesis of the External Genitalia Primordia. This can occur because of an embryologic error at 4 to 7 weeks of gestation. (23) The formation of the urorectal septum and differentiation of the cloacal membrane into the urogenital and anal membrane followed by rupturing to form the urogenital sinus and anus are imperative for genitourinary development. Cloacal dysgenesis will allow for the development of a small phalluslike structure, smooth perineum, and absence of urethral, vaginal, and anal openings. This leads to a male phenotype. This disorder can be associated with hydrops, oligohydramnios, prematurity, hydronephrosis, megacolon, colonic atresia, hyaline membrane disease, and pulmonary edema. (23) This can be seen in patients with VATER/VACTERL (vertebral defects–anal atresia–tracheoesophageal fistula with esophageal atresia–radial and renal dysplasia/vertebral defects–anal atresia–cardiovascular anomalies–tracheoesophageal fistula with esophageal atresia–radial and renal dysplasia–limb defects) syndrome.

Mayer-Rokitansky-Kuster-Hauser Syndrome. This is a syndrome caused by a mutation in the *WNT4* gene which is important in müllerian duct formation and steroidogenesis. (7) This disorder has an autosomal dominant pattern of inheritance with incomplete penetrance and variable expressivity. This phenotype leads to abnormal to absent müllerian duct structures with vaginal agenesis in XX females with normal ovaries. Urinary tract abnormalities, and occasionally, cervicothoracic somite dysplasia, may also be seen.

Neonate with an Abnormal Chromosome Number

Sex Chromosomal Abnormalities Leading to Gonadal Failure. The presence of more than 1 X chromosome, such as the XXY genotype seen in Klinefelter syndrome, will result in meiotic failure, loss of germ cells, and infertility. (24) Phenotypic findings may be present at birth such as small testes and micropenis, but these findings are more commonly identified during puberty. This disorder can also be associated with cryptorchidism and inguinal hernia.

45,X (Turner syndrome). These fetuses can form primordial follicles. As a result of the missing second X chromosome, ovarian development in affected fetuses will fail to complete a mature follicle and the oocytes will degenerate rapidly. Clinical features of patients with Turner syndrome include growth restriction, lymphatic changes (lymphedema), abnormal facies (low posterior hair line, downslanting epicanthal folds, low-set and posteriorly rotated ears), cardiovascular abnormalities (eg, coarctation of the aorta, bicuspid aortic valve), urinary tract abnormalities (eg, horseshoe kidney), and skeletal abnormalities (eg, scoliosis). (25) This condition may be diagnosed prenatally on ultrasonography with the identification of a neck mass or pleural or pericardial effusions.

EVALUATION OF NEWBORNS WITH DSD

When DSD is suspected in a newborn, formal evaluation should begin with a history and physical examination (Fig 2). Pertinent consultation with specialty teams such as endocrinology, urology, surgery, psychology, and/or social work should also be considered. Pertinent information to gather includes any test results obtained during the pregnancy, including a karyotype and any other genetic studies, as well as history of any assisted reproductive techniques that were used to conceive the neonate, because some conception procedures have been associated with urogenital defects. (10) Relevant maternal history includes a history of maternal virilization during pregnancy, which may potentially signal an aromatase deficiency or an androgen-secreting tumor, and any medication use during pregnancy. (26) Medications with significant androgenic action or effects include danazol, other exogenous androgens, or birth control and synthetic progestins. Other medications act as endocrine disruptors during pregnancy, such as the antiepileptic medications valproic acid, phenobarbital, topiramate, and phenytoin. A family history of other relatives with a history of DSD, abnormal genital development or abnormal puberty, infertility, hypospadias, or significant illness in the neonatal period should be noted. Perinatal findings such as fetal growth restriction or placental insufficiency have also been associated with abnormal genital development such as hypospadias. (27)

Physical examination of a neonate with suspected DSD should include evaluation of vital signs, with particular attention to the blood pressure, because both hypotension and hypertension may point to CAH secondary to 21-hydroxylase

deficiency or 11β-hydroxylase deficiency, respectively. Any midline defects or other dysmorphic features should be noted. Bony abnormalities can be seen in association with genetic conditions such as P450 oxidoreductase deficiency and *SOX9* gene deficiency, and may manifest as bowing of the long bones, limited elbow extension, (28) and craniofacial abnormalities such as craniosynostosis. (29) If CAH is suspected as a cause of genital ambiguity, hyperpigmentation of the nipple or genital area may be seen in the term or preterm newborn. The genital examination should systematically include evaluation for the presence of gonads, appearance of the labia or scrotum, phallus, and a urogenital examination. The scrotum should be evaluated for the presence of gonads, keeping in mind that any positive palpation of gonads may be either testicles, or more rarely, ovotesticles, which are abnormal gonads that contain both ovarian and testicular tissue. If the external genitalia are female in appearance, the labia should be evaluated for any abnormalities in separation, symmetry, the presence of any hyperpigmentation, any unusual swelling, and the presence of rugae. Any hernia should also be evaluated by bilateral palpation in females to check for the presence of testicles. In the term newborn female, a normal clitoral width is expected to be less than 6 mm, measured by gently pressing the shaft of the clitoris between the thumb and forefinger to exclude excess skin. The clitoris of a term newborn female measures 2 to 6 mm in width, and a width greater than 9 mm is considered abnormal. (10) The vaginal opening is visible when lifting the labia majora and should be an approximately 3 to 4 mm slit or stellate opening. The urethral meatus is an opening of approximately 1 mm ventral to the vagina. For the urogenital examination, any hypospadias and chordee should be noted in males, as well as any abnormalities in the position of the urethra in both sexes.

Preterm neonates may exhibit anatomic differences compared with the term neonate. The testes in the male preterm newborn may not have descended before 34 weeks' gestational age. Furthermore, the stretched penile length varies by gestational age, with an average length of 3.0±0.4 cm in newborns of 34 weeks' gestation or less, and 2.5±0.4 cm in newborns of 20 weeks gestation' or less. (10) The normal newborn clitoral length is 6.11±0.39 mm in term infants and 5.5±0.64 mm in preterm infants. (30) Mean width is 4.22±0.43 mm in term infants and 3.68±0.53 mm in preterm infants. (30) Preterm female neonates may have a more pronounced clitoris because of the decreased amount of adipose tissue deposited in the labia.

DIAGNOSTIC TESTING

Chromosomal evaluation is the first step in evaluation (Fig 2) of a neonate with ambiguous genitalia. Karyotype and fluorescence in situ hybridization for X and Y chromosomes

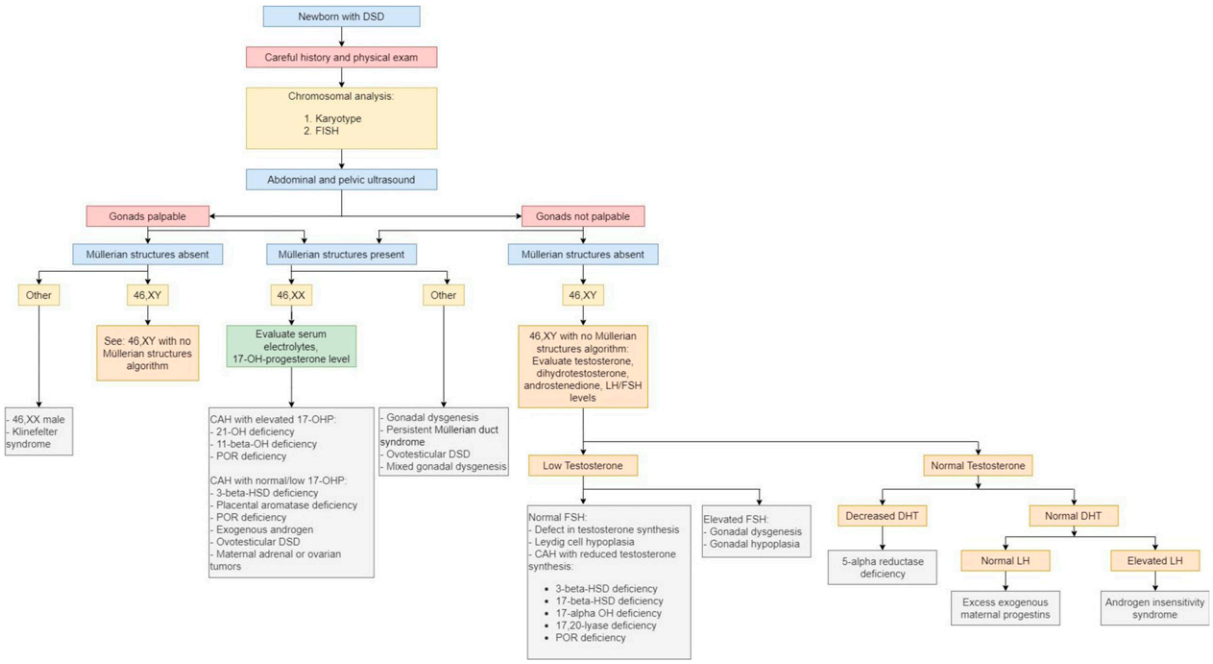

Figure 2. Diagnostic algorithm for DSD. CAH=congenital adrenal hyperplasia; DHT=dihydrotestosterone; DSD=disorder of sex development; FISH=fluorescence in situ hybridization; FSH=follicle-stimulating hormone; HSD=hydroxysteroid dehydrogenase; LH=luteinizing hormone; POR=cytochrome P450 oxidoreductase; 11β-OH=11β-hydroxylase; 17α-OH=17α-hydroxylase; 17-OH-progesterone=17-hydroxyprogesterone;17-OHP=17-hydroxyprogesterone.

TABLE. **Causes of Disorders of Sex Development**

CATEGORY	CAUSE	CLINICAL FEATURES
Gonadal dysgenesis	If male, gene mutations in *SOX9*, *SRY*, *LHCGR*	Male sex: Infertility, normal male or ambiguous genitalia
	If female, gene mutations in *FOXL2*, *WNT4*	Female sex: Bilateral streak gonads, hypoplastic ovaries, normal female external genitalia
	If either sex, *MX2*, *WT1*, *CBX2*, *NR5A1*, *GATA4*, *SIX1/4*, *CTNNB1*, *LHX9*	
Testosterone deficiency	Enzyme deficiency in converting cholesterol into testosterone and dihydrotestosterone (eg, 5-α-reductase-2 deficiency)	May have female appearance of genitalia, microphallus, cryptorchidism, abnormal fertility, cleft of the scrotum
Androgen receptor activity abnormality	Mutations in *AR* gene	Streak gonads, female phenotype with blind pouch vagina, breast development
Sex chromosome abnormality	XX female with X to Y translocation during paternal meiosis	XY translocation: Normal male internal and external genitalia with infertility OR ambiguous genitalia
	XO (Turner syndrome)	XO: Oocyte degeneration, growth restriction, lymphedema, cardiovascular abnormalities, urinary tract abnormalities, skeletal abnormalities
	XXY (Klinefelter syndrome)	XXY: Microphallus, small testes, cryptorchidism, infertility
Androgen excess	Exogenous androgen	Exogenous androgen: Clitoromegaly, labioscrotal fusion, regression of the urovaginal septum
	Placental aromatase deficiency	Placental aromatase deficiency: Clitoromegaly, labioscrotal fusion
	Congenital adrenal hyperplasia: • 21-hydroxylase deficiency • 11-β-hydroxylase deficiency • 3 β-hydroxysteroid dehydrogenase deficiency	• 21-hydroxylase deficiency: o Simple: Female can have virilization only evident by clitoromegaly, labial fusion, or penile hypospadias; male can have accelerated growth, skeletal maturation, early adrenarche o Salt-wasting: Adrenal crisis by 1 month of age with lethargy, vomiting, weight loss, hypoglycemia, hyperkalemia, hyponatremia, hypotension, ambiguous genitalia o Late-onset: Hirsutism, menstrual irregularity, early pubarchy or sexual precocity • 11-β-hydroxylase deficiency: Clitoromegaly, labial fusion, hyperpigmentation of genitalia, sodium retention and hypertension • 3-β-hydroxysteroid dehydrogenase deficiency: Clitoromegaly, labioscrotal fusion
Dysgenesis of external genitalia primordia	Embryology error at 4–7 weeks' gestation in the development of the urorectal septum and differentiation in the cloacal membrane	Labioscrotal swelling, phallus-like structure, may have absence of urethral and vaginal outlets Can be associated with VACTERL syndrome

VACTERL= vertebral defects, anal atresia, cardiovascular anomalies, tracheoesophageal fistula with esophageal atresia, radial and renal dysplasia, limb defects.

should be ordered, and generally have a turnaround time of 24 to 48 hours. These test results may allow for early sex assignment. (31)

Imaging such as ultrasonography of the abdomen and pelvis can be useful to determine the presence or absence of a uterus; however, it may be difficult to visualize ovaries on ultrasonography of the neonate. If the uterus is absent in a newborn who appears ambiguously female, it suggests the presence of testicular tissue producing AMH, suppressing female organ development. Ultrasonography of the adrenal glands in the setting of suspected CAH will demonstrate hypertrophy. (31)

Hormone levels should be measured 24 to 48 hours after birth because of the surge of androgens that usually occurs soon after birth. (31) Hormones such as testosterone, androstenedione, dihydrotestosterone, LH, and FSH should

be checked if gonads are palpable. If gonads are not palpable, 17-OHP, testosterone, and androstenedione levels should be measured to assess for adrenal abnormalities such as CAH. It is important to note that 17-OHP levels are higher in premature infants (median 38.7 nmol/L in neonates with a birthweight less than or equal to 1,500 g, 24.6 nmol/L in neonates of less than or equal to 2,000 g birthweight, and 20.1 nmol/L in infants with less than or equal to 2,500 g birthweight). (32) However, 17-OHP levels should be more than 80 times higher than the normal range in patients with 21-hydroxylase CAH. Most states now have newborn screening that includes the measurement of 17-OHP to allow for early identification; however, some cases may be missed if the newborn screening is performed before 24 hours of age because of early discharge requirements. Because of these missed cases, some states have moved to 2 screening tests, one in the nursery after birth and the second 8 days after birth. (33) As mentioned earlier, it is not prudent to check electrolytes until the second week after birth unless there are symptoms of salt-wasting. High urinary sodium concentrations can suggest a salt-wasting form.

COUNSELING PARENTS

Having a child with a DSD can be challenging for parents, and support from social workers and psychologists may be useful to the family. The infant's clinician should meet with the parents as soon as possible to discuss the evaluation. Ideally, a physical examination of the neonate with the parents should be performed for both educational purposes and parental bonding. The clinician should outline the consultations, laboratory testing, and imaging that will be required, and the timeframe in which the results will be available. Parents often wonder what to tell their friends and family, and what to expect for their child's future. Clinicians should encourage families to be honest with their support system within their comfort level. The clinical team should explain to the parents that the infant was born with a condition that is more common than people may think, and that tests will be performed to determine if the infant will more likely feel like a male or female. (34) Sex assignment can also be a challenging decision for parents. In general, most children with DSD will identify with the gender with which they were raised, but there is an increased incidence of gender dysphoria in children with DSD. (35)

CONCLUSION

Gonadal development is a complex genetic and hormonal process, and disruption of any step of the process can result in DSD. Ambiguous genitalia can be a sign of a life-threatening condition that may result in serious harm to the neonate if not quickly evaluated. Moreover, DSD can be psychologically challenging for both the parents and the child. Early detection of DSD and a systematic approach to diagnosis can lead to timely treatment and appropriate counseling of families.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Understand normal fetal sexual differentiation.
- Differentiate among disorders of sexual differentiation, know the etiology of abnormal sexual differentiation, and know the diagnostic approaches to and management of abnormal sexual differentiation.
- Know etiology and diagnostic approaches to an infant with ambiguous genitalia.
- Know the clinical manifestations, laboratory features, and therapeutic management of an infant with ambiguous genitalia.
- Know the causes of micropenis, including pituitary deficiency.
- Know how to evaluate and manage an infant with micropenis.
- Recognize the clinical manifestations and laboratory features of the various types of congenital adrenal hyperplasia.
- Define the appropriate therapy for the various types of congenital adrenal hyperplasia.
- Understand the basic enzymatic defects involved in the various types of congenital adrenal hyperplasia.

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