RadioGraphics

Evaluation and Management of Disorders of Sex Development: Multidisciplinary Approach to a Complex Diagnosis[1]

TEACHING POINTS
See last page

ONLINE-ONLY CME
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LEARNING OBJECTIVES

After completing this journal-based CME activity, participants will be able to:

- Describe the classification of DSD according to abnormalities of genetics, gonadal development, and androgen synthesis.
- Apply current terminology recommended by the European Society for Pediatric Endocrinology to describe DSD.
- Discuss a systematic approach to sex assignment based on clinical and imaging findings and biochemical measurements in patients with ambiguous genitalia.

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Various disorders of sex development (DSD) result in abnormal development of genitalia, which may be recognized at prenatal ultrasonography, immediately after birth, or later in life. Current methods for diagnosing DSD include a thorough physical examination, laboratory tests to determine hormone levels and identify chromosomal abnormalities, and radiologic imaging of the genitourinary tract and adjacent organs. Because of the complex nature of DSD, the participation of a multidisciplinary team is required to address the patient's medical needs as well as any psychosocial issues that the patient or the family may encounter after the diagnosis. The first step in the management of DSD is sex assignment, which is based on factors such as the genotype; the presence, location, and appearance of reproductive organs; the potential for fertility; and the cultural background and beliefs of the patient's family. The primary goal of sex assignment is to achieve the greatest possible consistency between the patient's assigned sex and his or her gender identity. Once the sex is assigned, the next step in management might be surgery, hormone therapy, or no intervention at all. Patients with ovotesticular DSD and gonadal dysgenesis may require a gonadectomy, followed by reconstructive surgery. Some patients may need hormone replacement therapy during puberty. An understanding of the immediacy of families' need for sex assignment and clinicians' need for reliable diagnostic imaging results will help radiologists participate effectively in the prenatal and postnatal assessment of patients with DSD.

Abbreviations: AIS = androgen insensitivity syndrome, CAH = congenital adrenal hyperplasia, DSD = disorders of sex development

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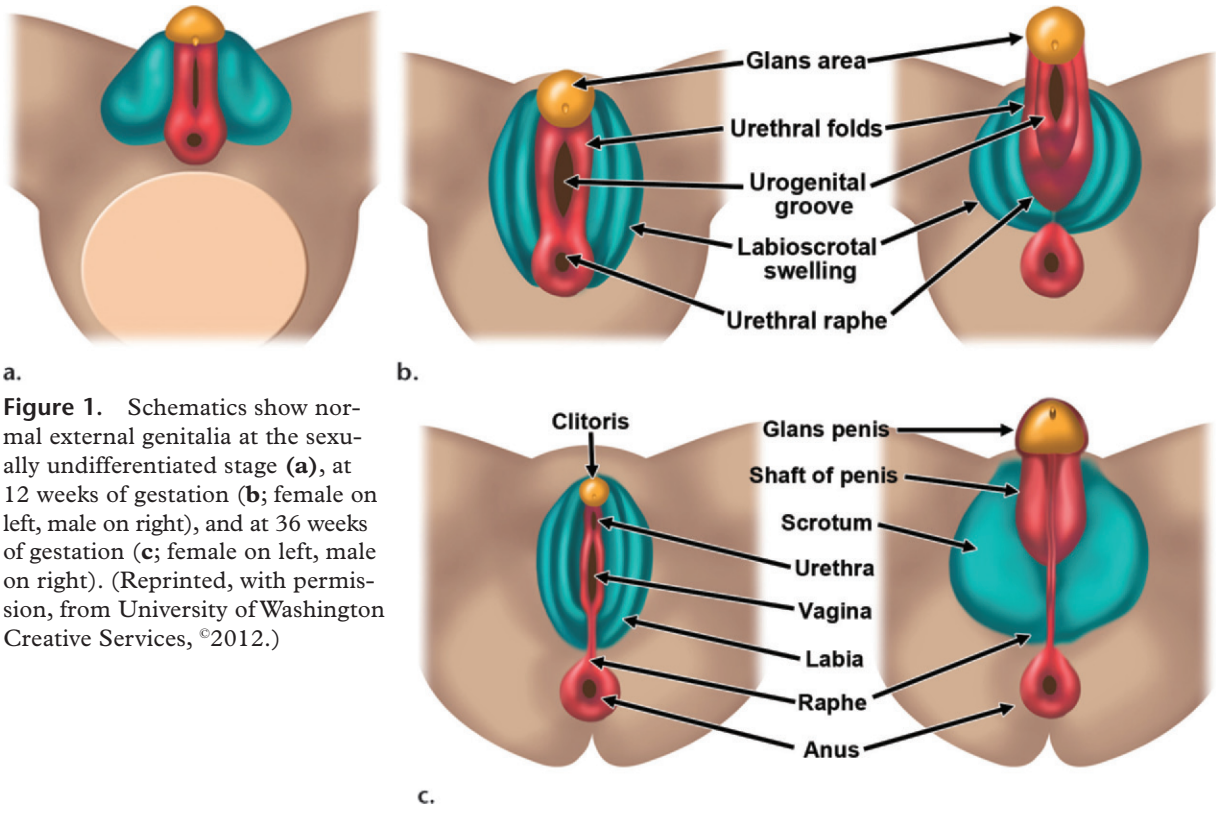


Figure 1. Schematics show normal external genitalia at the sexually undifferentiated stage **(a)**, at 12 weeks of gestation (**b**; female on left, male on right), and at 36 weeks of gestation (**c**; female on left, male on right). (Reprinted, with permission, from University of Washington Creative Services, ©2012.)

Introduction

Disorders of sex development (DSD) comprise a group of congenital conditions characterized by atypical chromosomal, gonadal, and anatomic sex development. The percentage of live births in which some aspect of DSD is seen has been estimated at 1%–2%, and only 0.1%–0.2% of those infants require corrective surgery at some point. Neonates with severe DSD resulting in ambiguous sexual differentiation are even less common (1). Most are treated at specialized medical centers by a multidisciplinary team consisting of a pediatric endocrinologist, pediatric urologist, pediatric radiologist, geneticist, and psychologist.

As part of the initial clinical assessment when the presence of DSD is suspected, imaging is performed to localize the gonads, determine the nature and structure of the internal sex organs, and detect any communication with external genital structures. Radiologists and radiologic technologists, including those who perform prenatal examinations, should be familiar with the imaging workup for DSD. Immediately after the diagnosis is confirmed, the infant's parents should be offered counseling and included in decision making (2). Sex assignment is dependent on many factors and should be postponed until a complete diagnostic assessment has been performed.

The article describes the pathogenesis of DSD and demonstrates the appropriate uses of diagnostic imaging in their evaluation and classification. An understanding of normal sexual development from primordial bipotential fetal structures is essential for appropriate investigation and management of DSD; thus, the article begins with a discussion of the normal development of the sex organs. A diagnostic algorithm for the prenatal and postnatal evaluation of DSD is presented, and sex assignment considerations and management options are described in detail, with consideration of ethical and psychosocial issues that may arise.

Normal Sex Development

Fetal chromosomes determine the genotypic sex. These chromosomes modify the primordial mesodermal cells by way of complex signaling pathways and hormones, with resultant cell differentiation into a phenotypic sex. The fetal adrenal glands originate from the same primordial mesodermal cells and develop synchronously with the fetal gonads (3). The sex-determining region Y gene (SRY gene) on the short arm of the Y chromosome initiates male sex differentiation. The testes produce testosterone, which stimulates the growth of wolffian structures, and antimüllerian hormone, which suppresses the development of müllerian structures. Male sex differentiation is accomplished by 12 weeks of gestation and is followed by growth of

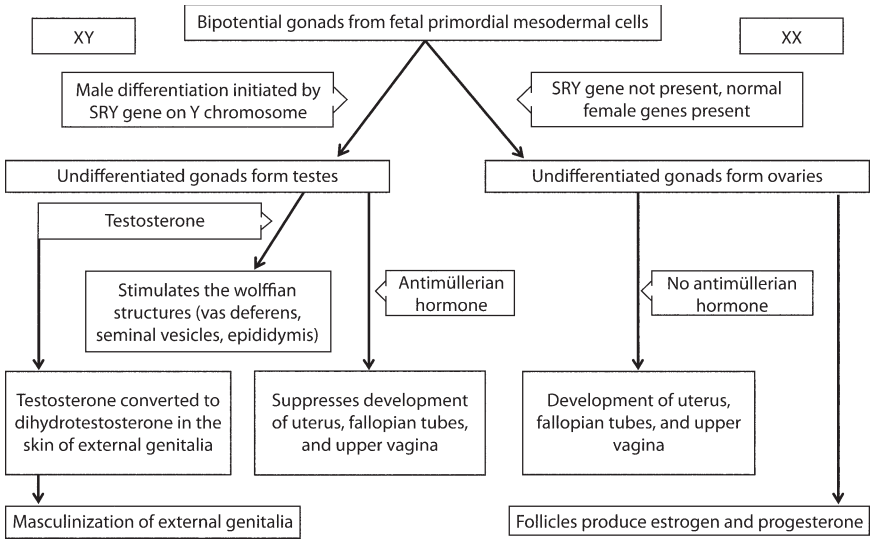


Figure 2. Flowchart shows the hormonal signaling pathways in normal sexual development.

Table 1
Revised Terminology for DSD

Old Terminology	New Terminology	Description
Intersex	DSD	Development of genitalia is abnormal
True hermaphroditism	Ovotesticular DSD	Both ovarian and testicular tissues are present; internal and external genitalia are ambiguous
XY sex reversal (XY female sex)	Complete gonadal dysgenesis	Streak (nonfunctional) gonads as well as müllerian structures are present; external genitalia are female
XX sex reversal (XX male sex), female pseudohermaphroditism	46,XX testicular DSD	Testes are present; internal and external genitalia are male
Male pseudohermaphroditism, XY male undermasculinization	46,XY DSD	Male gonadal development is abnormal; androgen synthesis or action is deficient; external genitalia are undermasculinized to a variable degree
Female pseudohermaphroditism, XX female overvirilization, XX female masculinization	46,XX DSD	Female gonadal development is abnormal; androgen synthesis or action is excessive; external genitalia are masculinized to a variable degree

Source.—Reference 2.

the penis and descent of the testes into the scrotal sac (4) (Fig 1). Historically, the development of the female phenotype was thought to occur by default when the SRY gene and downstream signaling pathways were not activated. More recently, however, unique genes (WNT4, RSP01, FOXL2) whose expression is required for normal female genital differentiation have been identified. A defect or mutation in any of the genes governing differentiation into a male or female phenotype can result in ambiguous genitalia (5,6) (Fig 2).

Classification of DSD and New Terminology

In 2006, a task force sponsored by the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society proposed a new nomenclature and classification system as well as new management recommendations for DSD (7). These disorders were further subdivided into 46,XY DSD (disorders of gonadal or testicular development and impaired androgen synthesis or action), 46,XX DSD (disorders of gonadal or ovarian development and androgen excess), and chromosomal DSD (numeric sex chromosome anomalies). There is some overlap between these three subgroups. This new terminology has replaced the older terms *hermaphroditism* and *pseudohermaphroditism* and emphasizes the genetic origin of the disorders (2) (Table 1).

Teaching Point

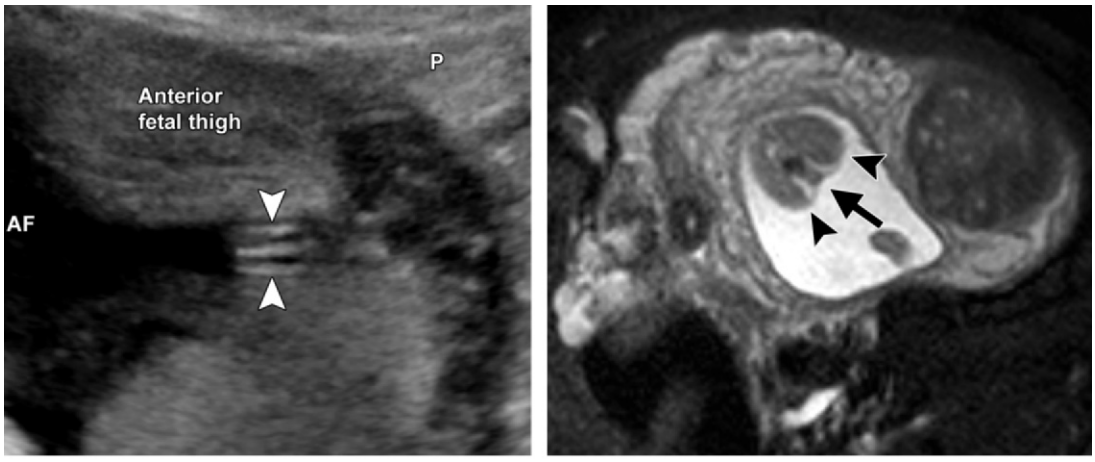


Figure 3. Appearance of normal female genitalia during the second and third trimesters. **(a)** Transverse US image obtained in a fetus at 26 weeks of gestation shows the expected appearance of three parallel echogenic lines, with the two outer lines (arrowheads) representing the lateral margins of the labial folds. *AF* = amniotic fluid, *P* = placenta. **(b)** Transversely oriented T2-weighted single-shot fast spin-echo magnetic resonance (MR) image obtained in the same fetus at 26 weeks of gestation for assessment of a placentation abnormality shows a linear region of signal in the midline that is isointense to the fetal soft tissue and muscle, a feature that represents the labia minora (arrow), with adjacent labia majora (arrowheads) surrounded by a region of high signal intensity.

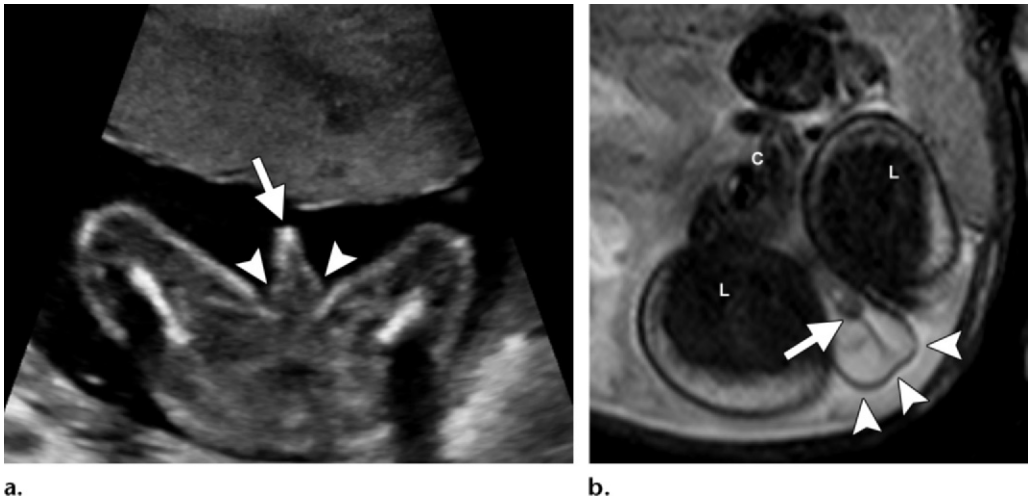


Figure 4. Appearance of normal male genitalia during prenatal development. **(a)** Transverse US image of a fetus at 18 weeks of gestation with legs abducted shows a normal penis (arrow) and scrotal margins that are rounded outward from the base of the phallus (arrowheads). **(b)** Axial T2-weighted single-shot fast spin-echo MR image of a fetus at 37 weeks of gestation shows the scrotal sac containing high-signal-intensity fluid (arrowheads) and a testis (arrow) with signal that is isointense relative to soft tissue and muscle. *C* = umbilical cord, *L* = fetal leg.

Prenatal Evaluation

The Society of Radiologists in Ultrasound and the American Institute of Ultrasound in Medicine recommend the assessment of fetal genitalia with radiologic imaging only when medically indicated and in twin gestations (8). In most obstetric practices, however, the status of fetal genitalia is routinely determined. Fetal genitalia can be visualized at 14 weeks of gestation with prenatal ultrasonography (US) performed by an experienced sonographer. The reliability of the US assessment of genitalia improves with increasing experience of the operator and increasing gestational age at imaging (9).

The transverse view is the most effective plane of imaging when the fetal legs are flexed, with the addition of oblique or tangential views if needed. Patience is required during the examination until

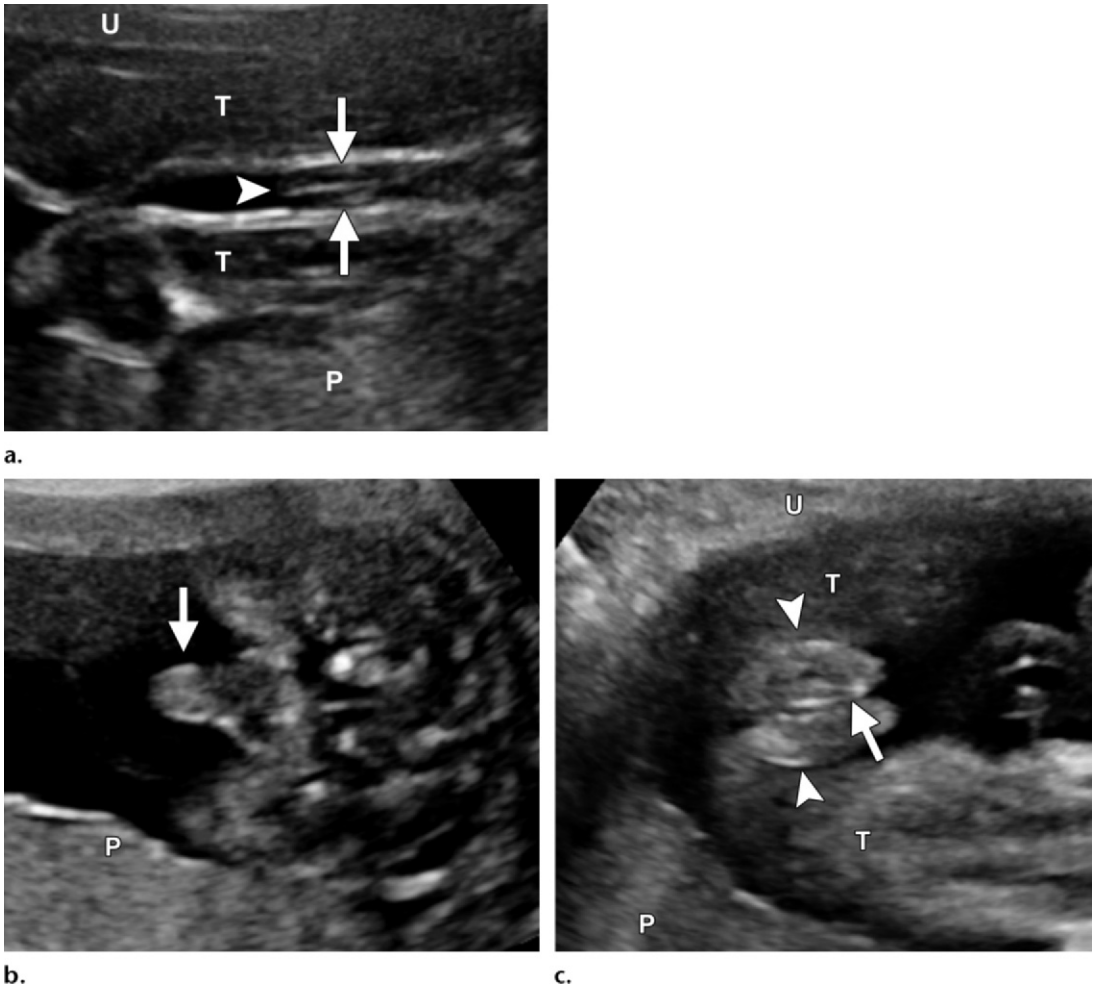


Figure 5. Pitfalls in US evaluation of fetal sex. **(a, b)** Transverse US images obtained in a male fetus at 22 weeks of gestation. With the fetal legs together, the scrotum (arrows in **a**) is compressed along the penis (arrowhead in **a**), mimicking labia. With the fetal legs apart, normal male genitalia are seen, with the penis clearly demonstrated (arrow in **b**). **(c)** Oblique transverse US image of a normal female fetus at 28 weeks of gestation shows a distorted appearance of the labia (arrowheads), which appear rounded, resembling a scrotum, and the fetal clitoris (arrow), which resembles a small penis. If the US beam is not angled correctly, distortion of the anatomy may result in misinterpretation. Note the similarity between this appearance and that shown in the prenatal US image in Figure 6, obtained in a fetus with an abnormal karyotype. *P* = placenta, *T* = fetal thigh, *U* = uterine wall.

the fetus is in the correct position for imaging. In approximately 60% of fetuses at 14–18 weeks of gestational age and in 80%–100% of fetuses after 20 weeks of gestational age, the genitalia can be accurately imaged (10). Visualization of fetal genitalia is improved with the use of three-dimensional US and virtual reality–enhanced (four-dimensional) US, which allows real-time three-dimensional visualization (10).

Teaching Point

At transverse US, female genitalia in the early second trimester appear as three parallel lines in the expected location between the fetal legs (Fig 3). During later gestation, the female genitalia appear as three bumps with the clitoris directed caudally in the midline. In the male, a small semicircular structure representing the scrotal sac is observed in the early second trimester, with the penis directed anteriorly and superiorly in the midline. From the late second trimester onward, the testes can be seen within the scrotum (9) (Fig 4). Errors in diagnosis may occur if the fetal legs are adducted or if the US beam is directed at the wrong angle (Fig 5).

Ambiguous genitalia should be suspected if the typical male or female genitalia are not seen at prenatal US. In such cases, a thorough fetal survey should be performed to detect possible associated anomalies (Figs 6, 7). Depending on the initial US findings and gestational age, repeat prenatal US and MR imaging examinations

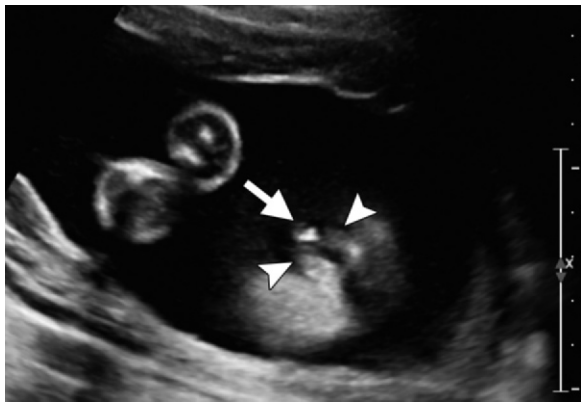
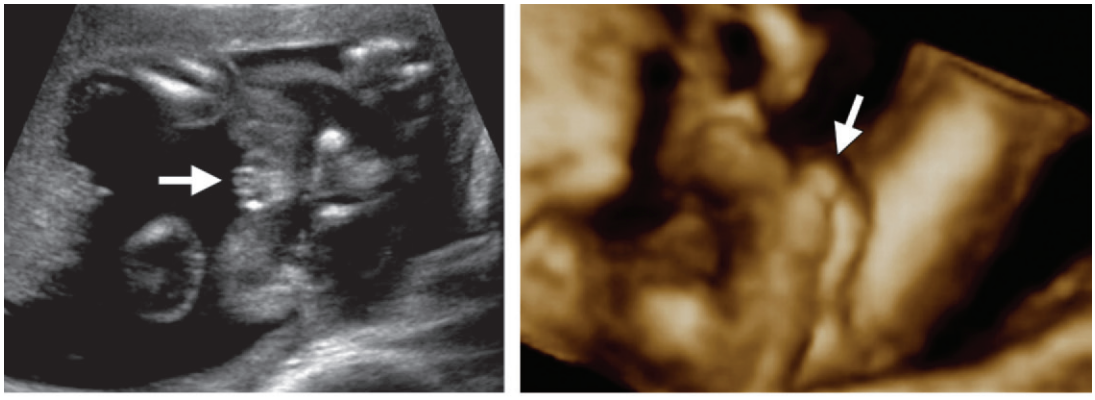


Figure 6. Ambiguous genitalia in a fetus at 24 weeks of gestation. A karyotype analysis of amniotic fluid obtained early in the pregnancy showed a complex mosaicism with triploidy 69,XXY/47,XY and trisomy 20. Prenatal transverse US image shows labia (arrowheads) separated by a prominent and elongated phallic structure (arrow) instead of the expected large clitoris. The parents decided to terminate the pregnancy. The pathologic diagnosis was ambiguous genitalia with a small penis and undescended testes.



a. b.

Figure 7. Ambiguous genitalia in a fetus at 20 weeks of gestation. Transverse **(a)** and three-dimensional **(b)** US images show a small phallic structure (arrow) and bifid small scrotum. Intrauterine growth restriction also was noted during this examination. A karyotype analysis of amniotic fluid obtained early in the pregnancy showed a 46,XY genotype. At autopsy after termination of the pregnancy, a micropenis and a midline depression of the scrotal raphe without an external opening were seen; the testes were undescended. No female genitalia were identified.

may be performed. MR imaging may be particularly helpful in cases of preexistent oligohydramnios or when multiple congenital abnormalities limit US assessment of the genitalia (11) (Fig 8). Recent studies by Nemec et al described the effectiveness of fetal MR imaging for demonstrating normal male and fetal genitalia, with excellent soft-tissue contrast and resolution (12,13). Along with imaging investigations, a fetal karyotype should be obtained for assistance in counseling parents in the prenatal period (3).

Postnatal Evaluation

In general, findings that should alert clinicians to possible DSD in neonates include bilateral nonpalpable testes, hypospadias in combination with a unilateral undescended testis or nonpalpable testes (which may also be associated with a cleft in the scrotal sac), clitoral hypertrophy, a foreshortened vulva with a single urogenital tract opening (also known as a urogenital sinus), and an inguinal hernia containing a gonad in a phenotypic female infant (3). Only 4%–7% of infants with DSD have ambiguous genitalia and indeterminate sex at birth (14). In 46,XX females, congenital adrenal hyperplasia (CAH) is the most common cause of DSD (1,4).

Clues to the diagnosis of DSD in older patients include the following conditions: unrecognized genital ambiguity, female inguinal hernia, delayed or incomplete puberty, female virilization, primary amenorrhea, phenotypic male breast development, and cyclical gross hematuria indicative of menstruation in a phenotypic male (15).

In all cases, a detailed family medical history should be obtained from the patient's parents. This history should include information about maternal exposure to toxins or drugs, previous

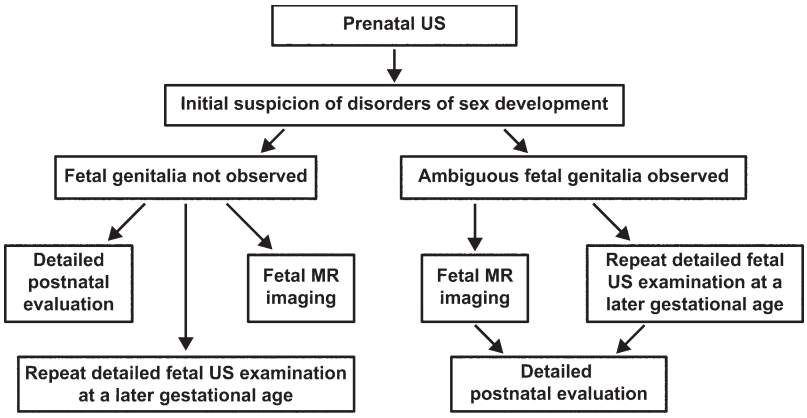


Figure 8. Flowchart illustrates a diagnostic imaging approach for further investigation of suspected prenatal DSD.

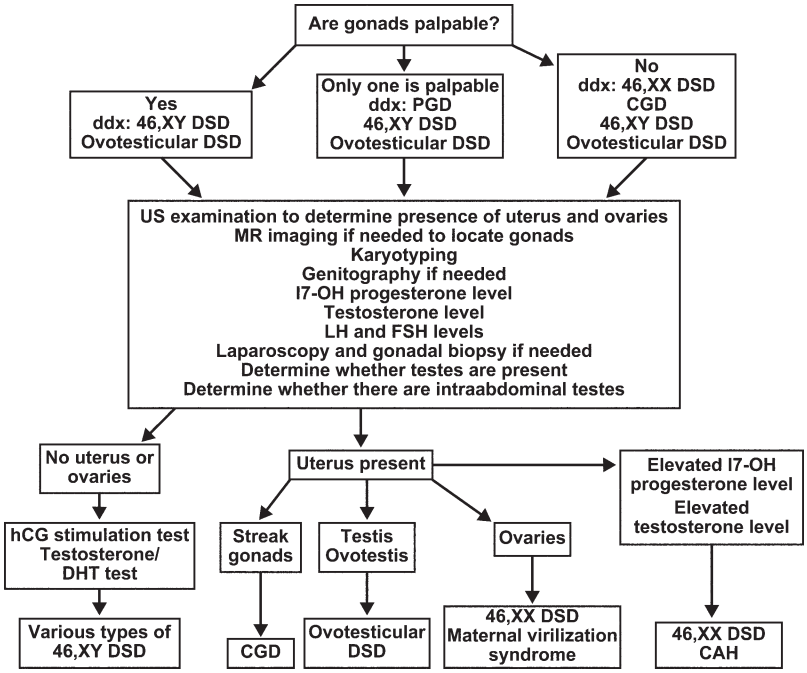


Figure 9. Flowchart shows an algorithm for diagnosing DSD by incorporating findings from karyotyping and other laboratory analyses, imaging studies, and physical examination. *CGD* = complete gonadal dysgenesis, *ddx* = differential diagnosis, *DHT* = dihydrotestosterone, *FSH* = follicle-stimulating hormone, *hCG* = human chorionic gonadotropin, *LH* = luteinizing hormone, *PGD* = partial gonadal dysgenesis.

neonatal deaths that could indicate some form of chromosomal abnormality or undiagnosed CAH, genital anomalies, abnormal pubertal development, and infertility (4).

Diagnostic Algorithm

Physical examination, laboratory tests, imaging studies, and in some instances, a surgical evaluation are performed in a coordinated approach to assess patients with DSD. A gonadal biopsy may be necessary as well (4,16) (Fig 9).

Physical Examination

A detailed physical inspection is the first step in the assessment of infants with ambiguous genitalia. The length of a penis or genital tubercle should be determined in its fully extended state and compared with normal parameters for a male or female infant (9,11). The presence of chordee may result in apparent foreshortening of the penis. Hypospadias or epispadias should be documented, along with the location of the urethral opening (11). The degree of fusion of the labioscrotal folds should be noted. The presence of only one urogenital opening or separate urethral and vaginal openings should be documented. In addition, pigmentation and thickening of the skin and the shape of the genital folds should be noted. The degree of virilization can be graded according to the Prader scale (3,11) (Fig 10).

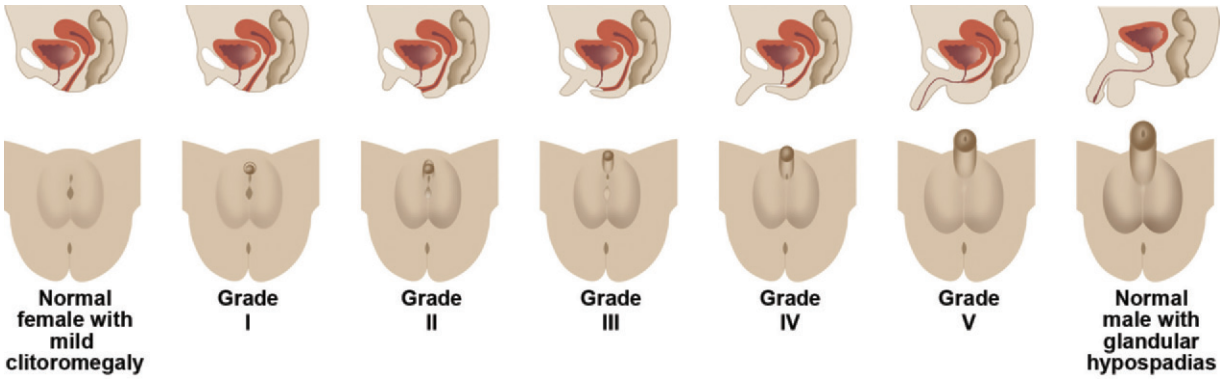


Figure 10. Schematics show the Prader system for classifying ambiguous external genitalia, with grades I–V describing increasing stages of virilization between a female phenotype with mild clitoromegaly at one end of the spectrum and a male phenotype with glandular hypospadias at the other end. (Reprinted, with permission, from University of Washington Creative Services, ©2012.)

Table 2
External Masculinization Scoring System

Score	Labioscrotal Fusion	Microphallus	Location of Urethral Meatus	Location of Right Gonad	Location of Left Gonad
3	Yes	No	Normal	…	…
2.5	…	…	…	…	…
2	…	…	Distal	…	…
1.5	…	…	…	Lower inguinal canal or scrotum	Lower inguinal canal or scrotum
1	…	…	Mid	Inguinal canal	Inguinal canal
0.5	…	…	…	Abdomen	Abdomen
0	No	Yes	Proximal	…	…

Note.—Status of fetal external genitalia is tabulated with this table on the basis of physical examination. The final score is calculated by using the left-hand column.

The external masculinization score is another grading system that may allow a more discriminating and objective assessment of the external genitalia. With this system, the masculinization of the external genitalia is quantified by assigning scores for labioscrotal fusion, microphallus, the location of the urethral meatus, and the presence and location of the gonads (11) (Table 2).

Because the absence of gonads and their number can dictate the next diagnostic step, localization with palpation, including in the inguinal region, should be attempted. If both gonads are palpable in the inguinal canal, they are likely testes or ovotestes (ie, gonads containing both types of germ cells); less commonly, they may be ovaries. If one gonad is palpable, it is likely either a testis or an ovotestis; a single ovary in the inguinal canal is a rare finding (6). In addition, the infant should be examined for other midline structural anomalies, such as a cleft lip or cleft palate, and for endocrinopathy, which may point to a pituitary-hypothalamic abnormality. If clinical evidence indicates that such entities may be present, an examination with MR imaging or another imaging modality should be considered.

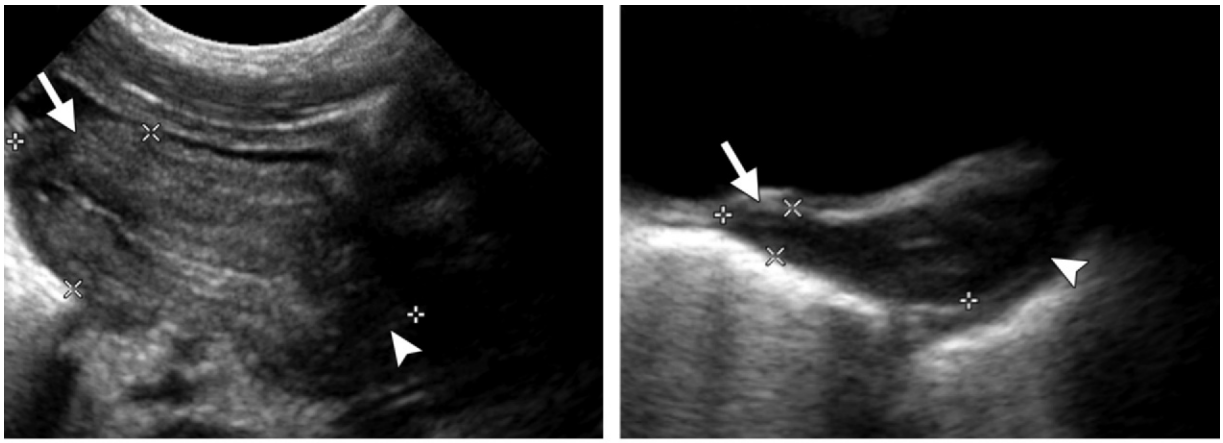
Laboratory Studies

Initial laboratory tests should include an immediate karyotype analysis for sex chromosome determination if gene sequencing and genetic mutation testing were not performed in the prenatal period. Depending on the results of karyotype and endocrine studies, additional tests such as gene sequencing for the androgen receptor and evaluations for 5α-reductase and 21-hydroxylase deficiencies may be indicated (16) (Table 3).

Table 3
Laboratory Tests and Diagnostic Findings in Infants with DSD

Test	Diagnostic Findings
17-hydroxyprogesterone level	Elevation is suggestive of CAH
11-deoxycortisol and 11-deoxycorticosterone levels	Both are elevated in 11-β-hydroxylase deficiency and depressed in 21-hydroxylase deficiency associated with CAH
Testosterone-to-dihydrotestosterone ratio*	A ratio of more than 20:1 is indicative of a 5α-reductase deficiency
Human chorionic gonadotropin stimulation	Nonresponse (ie, absence of increase in the testosterone level) is indicative of nonfunctioning Leydig cells, anorchia, or luteinizing hormone receptor defect
Antimüllerian hormone and inhibin B levels	Normal values in the postnatal period are suggestive of normal Sertoli cell function and the presence of at least one testis

*The ratio is determined when testosterone levels are normal.



a. b.

Figure 11. Expected changes in the neonatal uterus. **(a)** Sagittal image obtained in a female neonate on day 2 of life shows that the anteroposterior dimension of the uterine fundus (arrow) is similar to that of the cervix (arrowhead) because of the effect of maternal hormones on the fetus. **(b)** Sagittal US image obtained in a 3-month-old girl shows a global decrease in the size of the uterine fundus (arrow) relative to the cervix (arrowhead), approaching the typical premenarchal fundus-to-cervix ratio of 1:2.

Imaging Evaluations

Imaging examinations play a pivotal role in the assessment of a child's anatomy. US is the modality of choice, as it is easily accessible and does not require the use of radiation or contrast material. Genitography, voiding cystourethrography, and MR imaging are ancillary methods that may be useful for problem solving, clarification of the internal anatomy, and localization of nonpalpable gonads. In selected cases, panendoscopy, diagnostic laparoscopy under anesthesia, or both may be needed in addition to radiologic imaging to better delineate the internal anatomy.

Ultrasonography.—The imaging assessment of children with DSD begins with US of the kidneys; adrenal glands; pelvis; and inguinal, perineal, and anal regions. During the neonatal period, the uterus and ovaries are prominent because of maternal hormonal stimulation and thus can be easily found at US (17). The normal uterus appears tubular, with the anteroposterior diameter of the cervix matching that of the fundus; over a period of a few months, as maternal hormones are cleared from the infant, the thickness of the uterus diminishes (Fig 11). Neonatal ovaries may show several small follicles that gradually disappear. Normal neonatal testes appear homogeneous and isoechoic to hyperechoic at US (Fig 12) and gradually grow in symmetric fashion with age.

Figure 12. Normal testes in a full-term 46,XY infant with a prenatal diagnosis of ambiguous genitalia at US. Long-axis scrotal US images (**a**, right scrotum; **b**, left scrotum) show bilaterally descended testes. Pelvic US (not shown) revealed no uterus or ovaries. Karyotyping at amniocentesis showed a normal SRY gene, normal 7-dehydrocholesterol level, and normal androgen receptor sequencing. Postnatal clinical examination confirmed bilateral descended testes as well as an appropriately sized phallus and perineal hypospadias with penoscrotal transposition and chordee. The results of an extensive laboratory workup were negative for partial AIS. Male sex assignment was maintained, and hypospadias and chordee repair were performed when the patient was 1 year old.

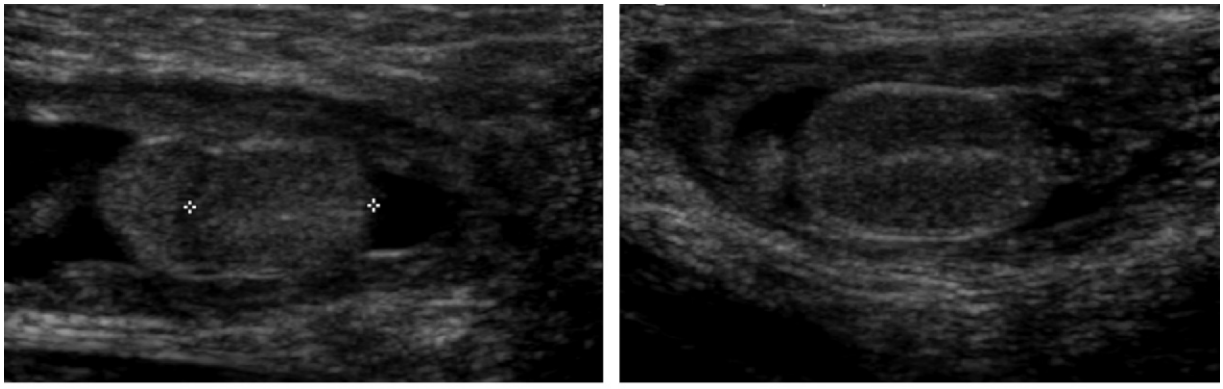


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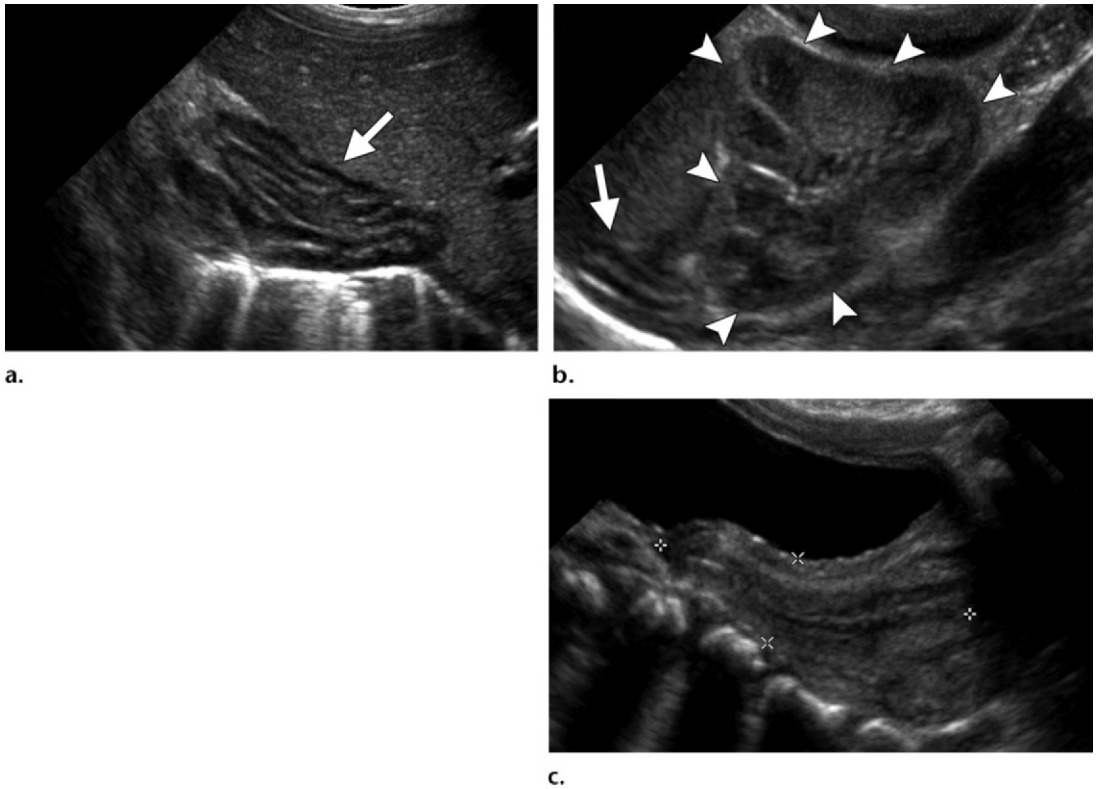
Figure 13. Enlarged adrenal gland in a full-term infant with ambiguous genitalia, including a small phallic structure, no meatus but a small orifice at the base of the clitoris, no palpable gonads, and fused labioscrotal folds. **(a, b)** Long-axis renal US images show a prominent right adrenal gland (arrow in **a**) and a normal-sized left adrenal gland (arrow in **b**) in an orthotopic position relative to the kidney (arrowheads in **b**). **(c)** Long-axis pelvic US image shows the expected appearance of the neonatal uterus (delineated by calipers). The left ovary (not shown) was also normal. No hydrometrocolpos was observed. A single cardiac ventricle was noted on an echocardiogram. Postnatal karyotype analysis showed 46,XX; SRY-negative status; and no deletion at 22q11 associated with velocardiofacial syndrome. Levels of 17-hydroxyprogesterone, dehydroepiandrosterone sulfate, 11-deoxycortisol, androstenedione, estradiol, follicle-stimulating hormone, and luteinizing hormone were normal. Subsequent laparoscopy showed two ovaries, a normal uterus, vaginal atresia, and a urogenital sinus. Female sex was assigned on the basis of gonads, genitalia, and genotype.



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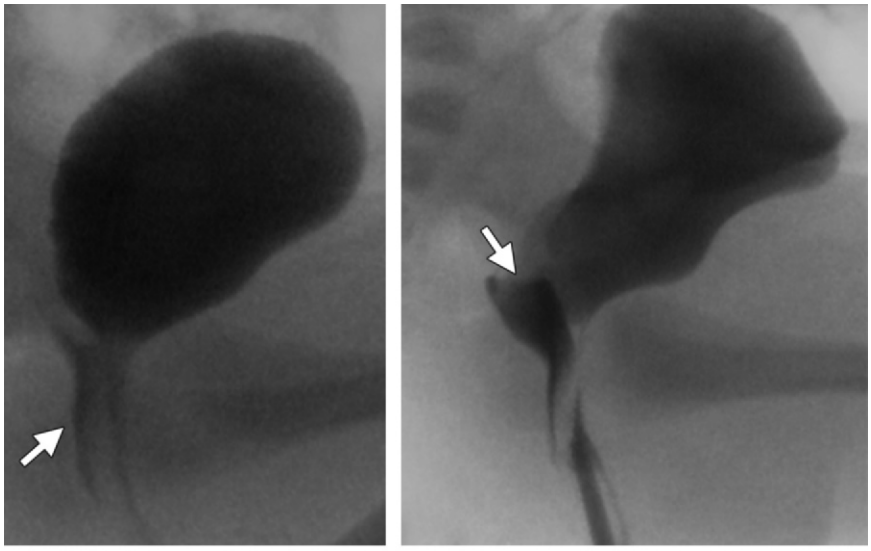
c.

Figure 14. Postnatal genitography in a neonate with ambiguous genitalia and a urogenital sinus with a single opening incorporating the vaginal and urethral orifices. An opening in the perineum was probed with an 8-F Foley catheter, and urine was returned. The catheter was advanced, and a voiding cystourethrogram was obtained. **(a)** Frontal oblique view demonstrates normal bladder contours and some filling of the vagina (arrow), findings indicating that the urethra and vagina open into a urogenital sinus. The infant voided several times, and the urethral contour appeared normal (not shown). The common opening was studied with sinography. **(b)** Lateral view shows contrast material, which was injected into the opening with a syringe, filling the bladder and an apparent vagina, with an impression (arrow) in the contrast material column that may be indicative of the cervix. No vesicourethral reflux was seen.



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The location and number of gonads in the pelvis or inguinal canal should be noted along with their echotexture. Adrenal gland size and texture should be assessed, and the gland surface should be examined for irregularities. The normal adrenal limb is less than 4 mm in width and less than 20 mm in length (18) (Fig 13).

Voiding Cystourethrography and Genitography.— Voiding cystourethrography and genitography are useful in defining the internal anatomy of the urethra, vagina, cervix, and urethrovaginal confluence. All perineal orifices should be examined. Proper technique includes lateral positioning of the patient with 90° flexion of the hips and use of an external radiopaque marker for calibrated measurement (18). A straight- or curved-tip catheter is inserted a short distance into each orifice, and contrast material is then injected in a retrograde direction (17).

Teaching Point

The presence of a fistula between the urethra and the vagina or rectum is identified with contrast material opacification. The presence and size of the vagina and the presence of a cervical impression in the contrast material column should be noted (Fig 14). If a urogenital confluence exists, its length should be measured, its relation to the perineum approximated, and its relation to the external sphincter noted (Fig 15). The degree of virilization is assessed by determining the ratio of the length of the horizontal anterior urethra to that of the vertical posterior urethra. In a normal male, this ratio is approximately 3:2. The presence of a verumontanum should also be noted (18).

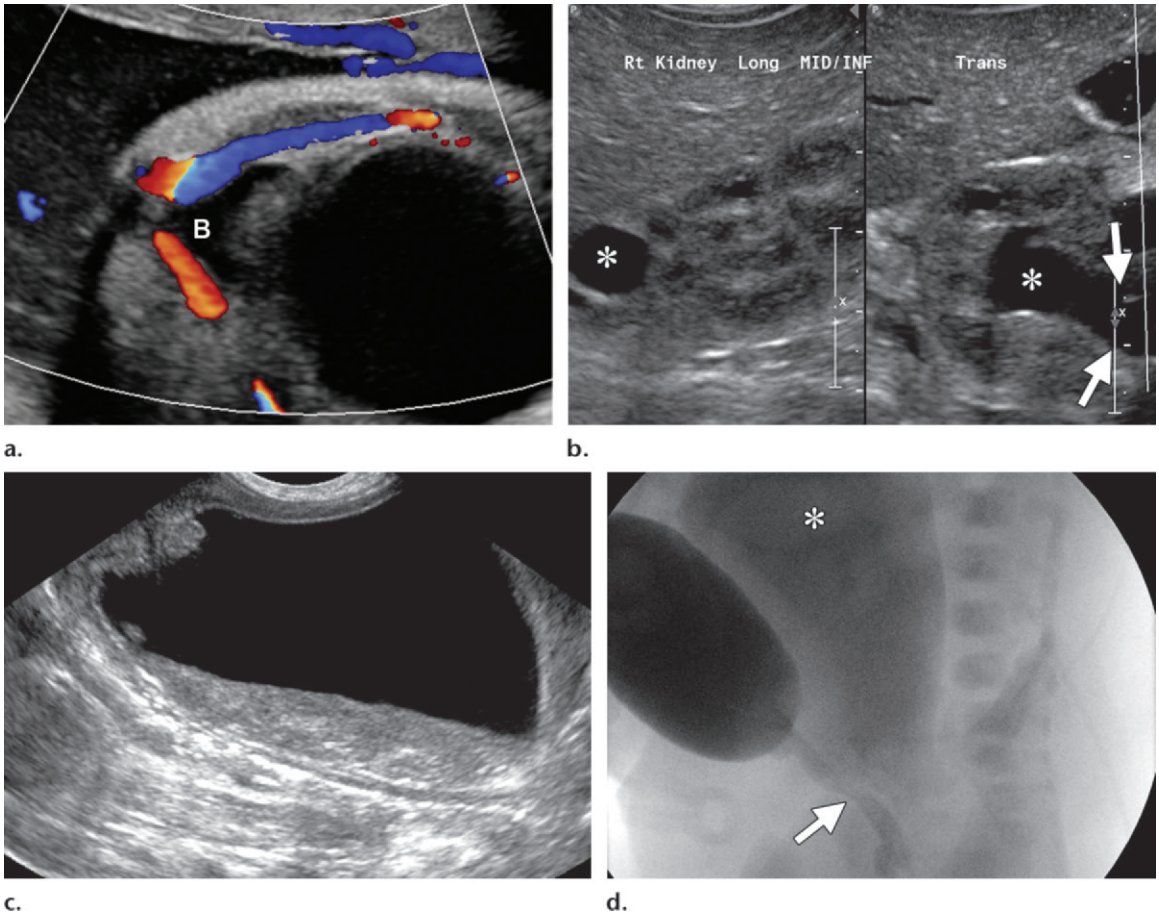


Figure 15. Cloacal variant in an infant with a prenatal diagnosis of ambiguous genitalia and an intraabdominal cystic mass. **(a)** Coronal prenatal US image obtained at 35 weeks of gestation shows an enlarged, thick-walled cyst centered in the pelvis, distinct from the bladder *(B)*; mild bilateral hydronephrosis and hydroureter were also noted (not shown). A clinical examination performed at birth showed fused labioscrotal folds and no clitoromegaly. **(b)** Postnatal longitudinal (left) and transverse (right) US images of the right kidney and ureter show bilateral pelviectasis (Society for Fetal Urology grade 3) (∗), ureterectasis (arrows), and a few scattered macroscopic cortical cysts. Similar findings were present in the left kidney and ureter. The adrenal glands were normal (not shown). **(c)** Long-axis pelvic US image shows a large fluid- and debris-distended structure posterior to the urinary bladder, which was decompressed with a Foley catheter at imaging. **(d)** Lateral voiding cystourethrogram obtained the 3rd day after birth shows a urogenital sinus (arrow) and dilute contrast material filling the cystic structure (∗) seen at US, a finding consistent with hydrometrocolpos. Cystoscopy and colposcopy revealed a 1.3-cm common channel and 2.5-cm urethra. Results of laboratory tests were negative for CAH. Female sex was assigned on the basis of a 46,XX genotype and anatomy.

MR Imaging.—MR imaging can provide more detailed anatomic information because of its superior tissue characterization and multiplanar capability. In a study by Kanemoto et al (19), 56 patients aged 1–12 years with a nonpalpable testis underwent US or MR imaging or both. US had a sensitivity of 76%, specificity of 100%, and accuracy of 84% for the detection of nonpalpable testes, whereas MR imaging had a sensitivity of 86%, specificity of 79%, and accuracy of 85%. US and MR imaging had equal sensitivity in depicting pelvic gonads, but MR imaging had

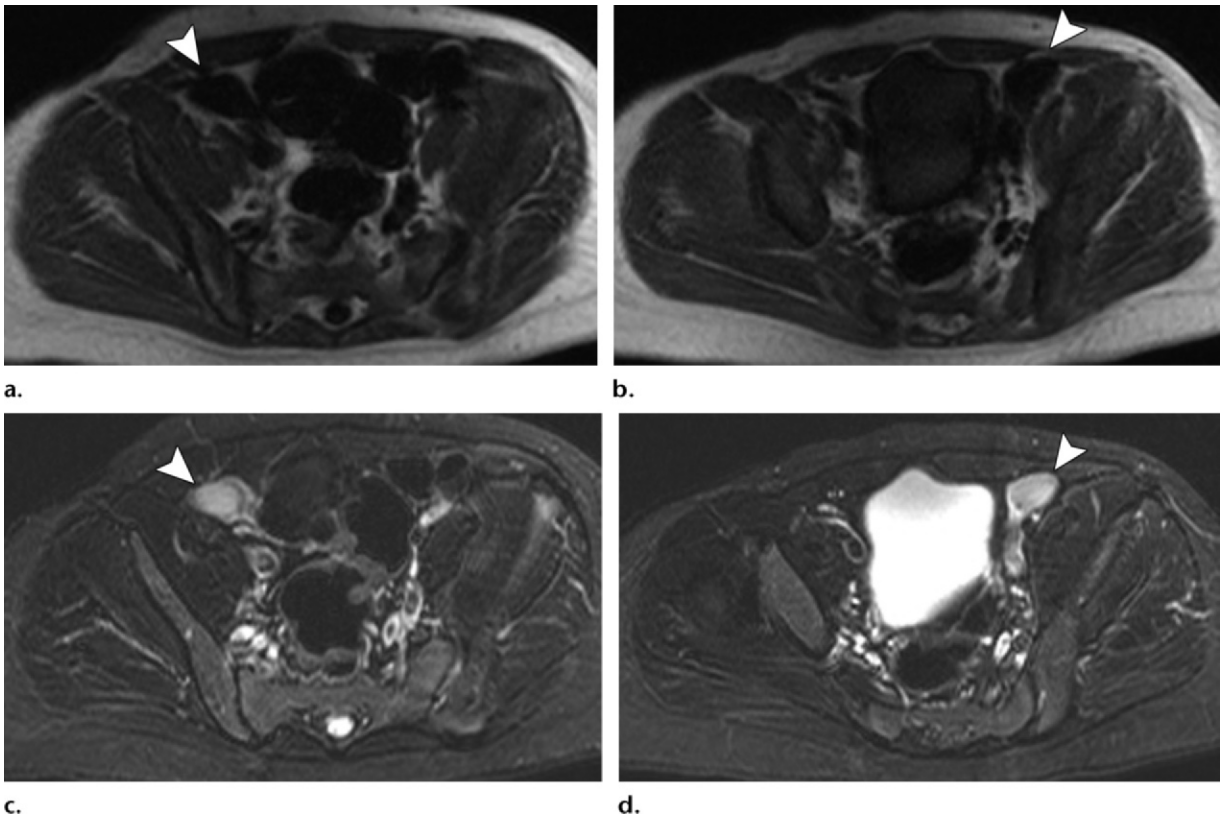
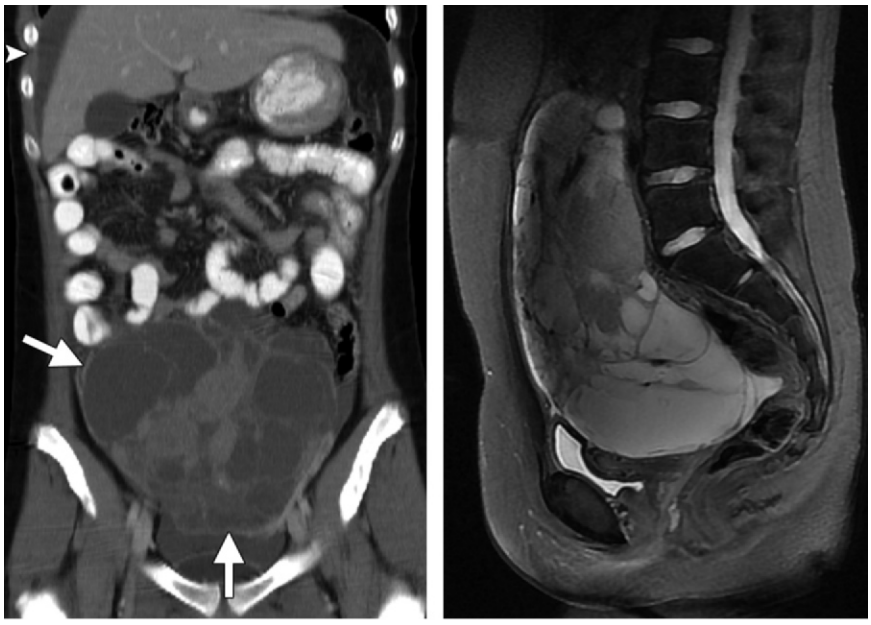


Figure 16. Ectopic testes in a 46,XY male with Pallister-Killian syndrome (also called tetrasomy 12p mosaicism or Pallister mosaic aneuploidy syndrome), an extremely rare genetic disorder resulting from an anomalous extra isochromosome at 12p, the short arm of chromosome 12. In infancy, the patient had presented with a congenital diaphragmatic hernia and undescended testes. Abdominal MR imaging was performed at the age of 16 years to verify the presence and location of the testes. Axial MR images obtained in the upper pelvis show well-marginated bilateral intraabdominal testes (arrowhead) with homogeneous low T1-weighted signal intensity (**a**, right testis; **b**, left testis) and homogeneous high T2-weighted signal intensity (**c**, right testis; **d**, left testis).

greater sensitivity than US for the localization of intraabdominal gonads (19). Ectopic gonads, testes, and noncystic immature ovaries have uniform high signal intensity at T2-weighted MR imaging. Ectopic gonads may show low signal intensity centrally and intermediate signal intensity along the rim or homogeneous low signal intensity at T1-weighted imaging (Fig 16). Streak gonads (those with nonfunctional germ cells) are difficult to detect with any imaging modality, including MR imaging, and are typically identified laparoscopically. At T2-weighted MR imaging, they may contain low-signal-intensity stripes. Foci of high signal intensity in streak gonads at T2-weighted imaging are suggestive of malignant changes (17,20). MR imaging can also be used in staging when complications such as malignancy are suspected (21).

Computed Tomography.—Computed tomography (CT) is the modality of choice for imaging evaluations of DSD-associated malignancies and staging of germ cell tumors (Fig 17). CT is also useful for evaluating postoperative complications such as hematoma and abscesses that arise because of sex reassignment procedures or tumor resection (21).



a. b.

Figure 17. Germ cell tumor and streak gonad in a 17-year-old 46,XY female with progressive abdominal pain. The patient had presented at 15 years of age with primary amenorrhea, female external genitalia, and tall stature. Hormone levels revealed hypergonadotropic hypogonadism, and primary hormonal therapy was initiated. **(a)** Coronal CT image obtained with oral and intravenous contrast material shows a small volume of free fluid with attenuation of 20–50 HU (arrowhead) and a large mixed cystic and solid mass (arrows) arising from the pelvis and extending superiorly into the lower abdomen. No intraabdominal adenopathy or peritoneal nodularity was found. **(b)** Sagittal T2-weighted MR image shows numerous intratumoral septations and solid components. The mass is separate from the urinary bladder and uterus. At resection, the mass was found to be a stage IA mixed germ cell tumor. A left streak gonad was also resected.

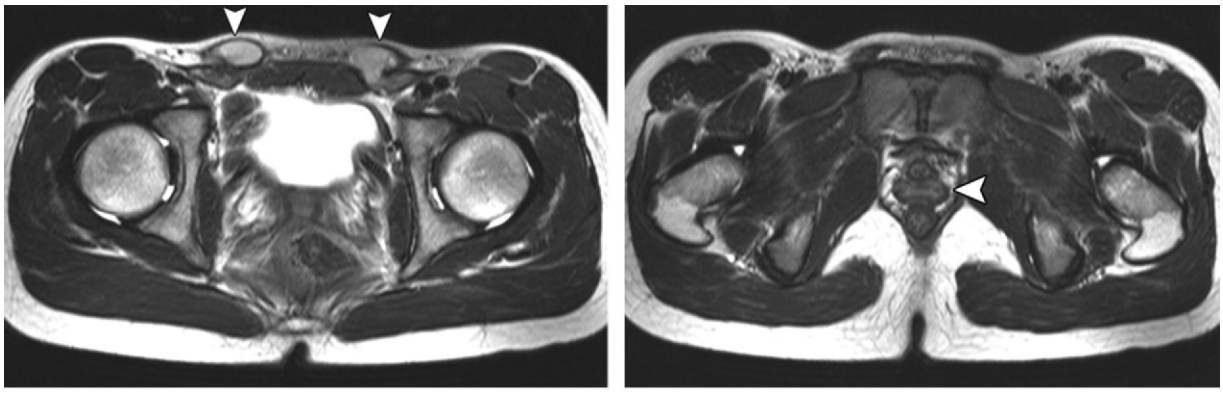
Sex Assignment

Teaching Point

All infants affected by DSD must be assigned a sex of rearing. The following factors play a crucial role in the complex process of sex assignment: diagnosis, karyotype, appearance of the external genitalia, type of gonads present, need for surgical interventions to provide consistency with the sex of rearing, use of hormonal therapy, potential for fertility, parental wishes, and parental cultural beliefs. Knowledge of the cause of the disorder can aid in determining sex assignment for patients with a 46,XX genotype and CAH, a 46,XY genotype and complete gonadal dysgenesis, or a 46,XY genotype and complete androgen insensitivity syndrome (AIS) (22,23).

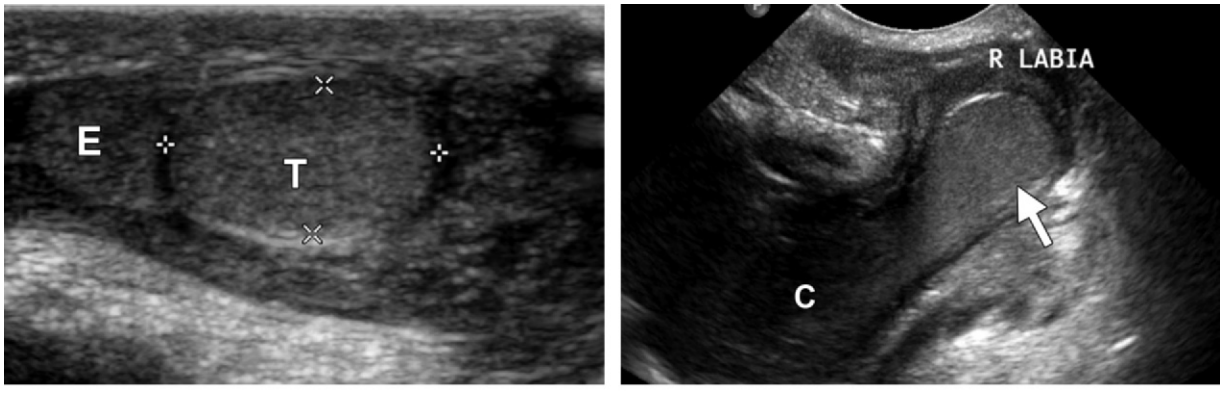
Almost all infants with 46,XX-related CAH are raised as females; they have the potential for fertility, and they identify with the female gender as adults. However, a few infants with 46,XX-related CAH are raised as males and maintain male self-identification as adults (24). Infants with a 46,XY genotype and either complete AIS or complete gonadal dysgenesis have complete female external genitalia and are raised as females (25) (Fig 18). As adults, they identify with the female sex. Women with complete gonadal dysgenesis have a uterus and can be impregnated with donor oocytes (26). Currently, 46,XY infants with a micropenis are raised as males because no surgical intervention is needed; there is the potential for fertility, and their gender satisfaction appears to equal that of patients with the same disorder who are raised as females (27). This practice contrasts sharply with the previously prevalent belief that such infants should be raised as females (28).

Among patients with a 5α-reductase deficiency, phenotypes range from female external genitalia to undermasculinized male external genitalia (29) (Fig 19). It can be difficult in such cases to determine the sex of rearing. Mendonca et al (30) reported that 50% of patients with a 5α-reductase deficiency who were raised as females later self-identified as males.



a. b.

Figure 18. Complete AIS in a 16-year-old 46,XY female with primary amenorrhea and absence of the cervix at clinical examination. Normal labia majora and minora and palpable intracanalicular gonads were found at physical examination. Pelvic US (not shown) demonstrated the absence of a uterus and ovaries. **(a)** Axial T2-weighted MR image shows homogeneous high-signal-intensity structures (arrowheads) representing testes in the anterior lower pelvic wall near the labia. **(b)** Axial T2-weighted MR image obtained in the lower pelvis shows the lower vagina (arrowhead) between the anorectal junction and urethra. Orchiectomy was performed, and pathologic evaluation showed cryptorchid testes with Leydig cell hyperplasia, inactive tubules, and smooth muscle hypertrophy of the spermatic cord.

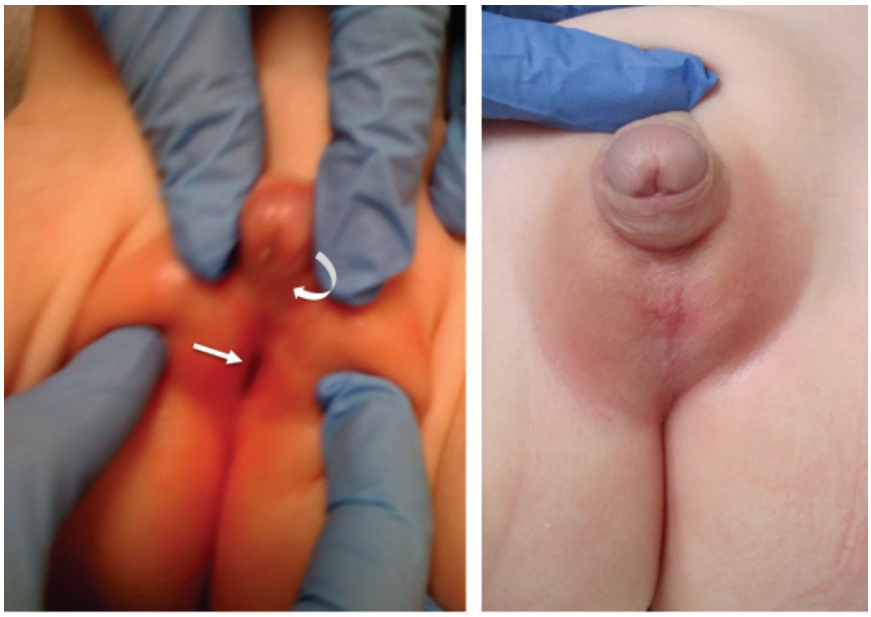


a. b.

Figure 19. Infant with a 5α-reductase deficiency due to a homozygous mutation. At birth, the patient had genital ambiguity, with palpable gonads within prominent labia majora. **(a)** Long-axis pelvic US image shows a testis and associated epididymis within the left labial fold (right testis and epididymis not shown). *E* = epididymis, *T* = testis. **(b)** Long-axis pelvic US image shows a uterus with extension toward the introitus. Hydrometrocolpos is evidenced by homogeneous hemorrhagic material (arrow) within the uterine cavity and vagina (arrow; *C* = cervix). The kidneys were orthotopic (not shown). Genetic and laboratory test results revealed a 46,XY genotype, and fluorescence in situ hybridization analysis showed one SRY locus on the Y chromosome. Results of laboratory analyses excluded CAH. Elevated levels of antimüllerian hormone (104 ng/mL; normal range = 0–7.1 ng/mL) and inhibin B (60 pg/mL) indicated the presence of functional Sertoli cells in the gonads, and the testosterone level was 110 ng/dL, making a diagnosis of gonadal dysgenesis less likely. No androgen receptor defect was identified. Female sex was assigned on the basis of external genitalia and parental preference. At pathologic analysis, the resected gonads were identified as prepubertal testes. Further genetic testing showed a 5α-reductase deficiency.

Sex assignment for patients with partial AIS and partial gonadal dysgenesis is fraught with even more difficulties. Approximately 25% of such patients are dissatisfied with their assigned sex, whether it is female or male (31).

The assigned sex of rearing in cases of ovotesticular DSD depends on the potential for fertility, the appearance of the external genitalia, and the type of surgical intervention needed to achieve the preferred phenotypic sex. Infants with 45,X/46,XY mixed gonadal dysgenesis are usually assigned the sex most consistent with the testicular function observed prenatally and predicted at puberty and with the external masculinization score (32).



a. b.

Figure 20. Hypospadias in an infant with a 46,XY genotype and ovotesticular DSD. **(a)** Preoperative photograph shows mild penoscrotal transposition (the two halves of the scrotal sac are lateral to the base of the penis), with the phallus approximately 3 cm long and showing chordee (curved arrow). An intact vaginal opening (straight arrow) and a urethra are visible. A uterus was seen at US (not shown). At bilateral gonadectomy (performed at the age of 7 months), histopathologic analysis showed mixed gonadal dysgenesis. At the age of 22 months, the patient underwent surgical reconstruction of the genitalia with chordee release, hypospadias repair, and scrotoplasty. **(b)** Postoperative photograph of the same patient shows the appearance of the male genitalia after surgical reconstruction.

Management of DSD

Discordance between chromosomal, gonadal, and phenotypic sex of children with DSD determines the course of management and type of treatment considered. In patients with DSD, the three components of psychosocial development—gender identity, gender role, and sexual orientation—may not always be congruent. These issues have resulted in fundamental changes in sex assignment in recent years. The primary goals are for gender identity to be consistent with sex assignment and to reduce gender dysphoria, the feeling of being the opposite gender to which one was born or assigned and wanting to live as that opposite gender. To improve the poor outcomes associated with previous management of DSD, emphasis has recently been placed on the use of prescribed guidelines and consideration of cultural background and parental input in clinical decision making (33).

Surgical Procedures

Surgical reconstruction of the external genitalia depends on the final sex assignment. The goals of surgery should be cosmetic improvements and preservation of function or sensitivity of the genital region. Current recommendations encourage emphases on function over cosmetics, realistic expectations, and parental understanding of potential short- and long-term consequences of suggested surgical procedures and the alternatives (25). Outcome studies showed decreased sexual sensitivity and sexual function in patients with CAH who were assigned female sex and underwent feminizing genital surgical procedures with vaginal reconstruction during infancy (34). Various vaginoplasty techniques may result in vaginal scarring at the introitus, which may require repeated surgical modifications. Although rare, surgical reconstruction of a neovagina from a bowel segment has been associated with the development of carcinoma in the graft. The pathogenesis of such tumors is not yet clear, but they are hypothesized to arise because of chronic irritation resulting in intraepithelial neoplasia (2,35). Many investigators have suggested that although feminizing genitoplasty performed in infants may result in immediate cosmetic benefits, it may not effectively con-

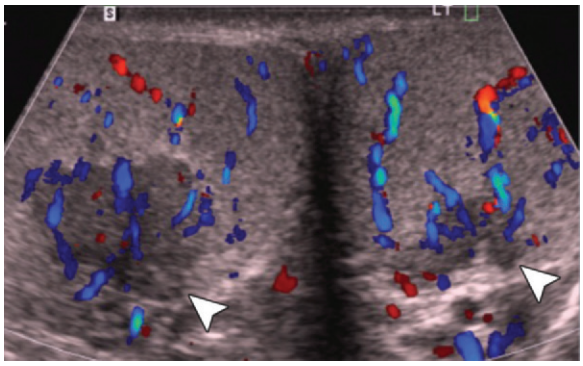


Figure 21. Transverse color Doppler flow US image obtained in a 26-year-old man with known CAH shows adrenal rests (arrowheads) with mildly increased vascularity in both testes. Recognition of this condition is important in order to avoid unnecessary orchiectomy or biopsy.

tribute to stable gender identity or psychosocial development. As a result, clitoroplasty with preservation of the neurovascular bundle is recommended only for those with the most severe clitoromegaly. For those with less severe conditions, clitoroplasty and vaginoplasty are usually deferred until later in life unless there are medical complications (36).

For 46,XY males with hypospadias or undescended testes, surgery is initiated at the age of 6–12 months, with the goal of completing all stages of hypospadias repair by 2 years of age (37) (Fig 20). In infants with dysgenetic gonads, gonadectomy is recommended as soon as possible to decrease their risk for neoplasms. In 46,XY females with complete AIS, the risk of gonadal malignancy before puberty is lower, allowing the option of gonadectomy later in life. The retained gonads produce testosterone, which is converted to estrogen, assisting in the induction of spontaneous breast development without the use of exogenous estrogens. However, those with partial AIS who are raised as females undergo gonadectomy to avoid virilization at puberty (25). Of note, the currently available literature reflects surgical management procedures practiced 10–20 years ago for patients with DSD. The long-term outcomes of current standard surgical techniques continue to be evaluated.

Pharmacologic Therapies

In patients with an androgen synthesis disorder or androgen action deficiency who are raised as males, treatment with testosterone injections may help to increase penile size. Pharmacologic hormone replacement therapy is also essential (6). Hypogonadism is common in patients with gonadal dysgenesis, and hormonal induction of puberty may be required. In such cases, intramuscular injections of testosterone esters are administered in males and estrogen supplements are given to females, with progesterone usually added to induce menses in females with a uterus (2).

Malignant Potential

As a group, patients with DSD have an increased risk for gonadal malignancies, particularly germ cell tumors such as seminomas, dysgerminomas, and nonseminomas. The risk appears to be higher in those with an XY genotype and undermasculinization (38).

Overall, 20%–30% of children with 46,XY complete gonadal dysgenesis and 15%–20% of those with mixed gonadal dysgenesis develop malignancies within the 1st to 2nd decade of life; therefore, streak or dysgenetic gonads should be removed. Those with Klinefelter syndrome, a disorder characterized by a 47,XXY genotype, have increased risks for germ cell tumor of the mediastinum, testicular stromal tumor, and breast malignancies (17,39).

Teaching Point

Gonadoblastomas are the most common tumors arising from intraabdominal or intrapelvic gonads, with a 25% rate of occurrence (40). These tumors are considered precursors to malignant seminomas and nonseminomatous germ cell tumors. On US images, an echogenic focus associated with the pelvic organs or in an ectopic gonad or labioscrotal fold should be investigated, as gonadoblastomas are often calcified. They may appear as solid tumors on CT or MR images and may be associated with hemorrhagic ascites (Fig 17). In cases of a contralateral streak gonad or undescended gonad, there is an increased risk of bilateral tumor development. The treatment for gonadoblastomas is gonadectomy (40).

Adrenal rests may be identified in the testes, appearing as homogeneous hypoechoic noncalcified tissue that may show mildly increased vascularity at US. Adrenal rests do not cause any architectural distortion of the testes and can have variable appearances at follow-up US examinations. This condition affects males with CAH, in whom the suppression of adrenal androgens is inadequate (41) (Fig 21). These patients also have an increased risk for Wilms tumor, especially in the setting of XY gonadal dysgenesis associated with glomerulonephropathy (Denys-Drash syndrome) (17,38).

Table 4
Ethical Guidelines for the Management of DSD

Ethical Principle	Management Steps
Minimize physical risks	Monitor patients for gonadal cancer, osteoporosis due to refusal of sex hormone replacement therapy, adrenal crisis, urinary tract infection, and outflow obstruction
Minimize psychological risks	Address issues of gender identity dysphoria, poor parental bonding, and social isolation
Preserve potential fertility	Use assisted reproductive technology as required
Preserve ability to have satisfactory sexual relationships	Maintain sensorineural vascular supply and gonads containing germ cells, use available fertility preservation techniques, use existing structures if in utero pregnancy potential exists, and preserve or enhance capacity for satisfying sexual relations
Respect parental desires and beliefs	Discuss with parents their social, ethical, and religious preferences

Sources.—References 44, 45.

Psychosocial Issues

Counseling Services

A psychologist, preferably one with experience with DSD, should be in contact with the patient and family from the outset. The parents of infants with DSD are often overwhelmed by the diagnosis and may need help in verbalizing their concerns and in developing coping skills. They also may need guidance for explaining the condition to their child and others. The psychologist should cultivate an ongoing relationship with the child and family as part of the management plan (32).

The psychologist can help parents explain the diagnosis to their child in an age-appropriate way and plan later, more detailed disclosures about the karyotype, gonadal effects, and issues of fertility. The concepts of fertility and infertility can be introduced to the child and discussed in the natural context of daily activities. The psychologist can also determine if the family is having difficulties with the diagnosis and if additional support is needed. Access to support groups or the ability to speak with other families affected by DSD may be helpful. The psychologist can also monitor the child for gender dysphoria or social isolation (42). To our knowledge, long-term outcome studies are available for only a few DSD, and thus the true incidence of gender dysphoria and social isolation is not well known. In a study of 250 patients with 46,XX CAH (one of the most frequently studied causes of DSD), gender dysphoria was found in 5.2% (23). By comparison, only 0.008% in the general population are reported to be affected by gender dysphoria (43).

Adolescence is a difficult time even for children without DSD. The psychologist can give adolescents with DSD the opportunity to discuss their thoughts about gender identity, sexuality, sexual orientation, and relationships in a safe and nurturing environment.

Ethical Considerations

Ethical issues in the management of DSD are evolving. The Fifth World Congress on Family Law and Children's Rights met in Halifax, Nova Scotia, in August 2009 and endorsed the guidelines proposed by an Australian multidisciplinary team of specialists in DSD. These ethical principles, which are summarized in Table 4, can be used as a guide for planning the care of patients with DSD, determining the sex assignment, assessing the need for surgery, referring the patient and parents for appropriate follow-up counseling, and scheduling necessary hormone replacement therapy (44,45).

Conclusions

DSD describes a group of complex conditions that require coordinated assessment and management by a multidisciplinary team of specialists. This field is undergoing rapid development and has evolved into an area of active clinical investigation. Goals for future research include identification of the genes involved in the pathogenesis of each disorder. Better long-term outcome studies are needed to evaluate the effectiveness of current methods of treatment.

Radiologists involved in neonatal and prenatal imaging of patients with DSD play an important role in diagnosis and treatment planning. US is the primary imaging modality, with genitography, voiding cystourethrography, MR imaging, and CT playing ancillary diagnostic roles. Sex assignment is a delicate process that requires consideration of multiple factors and a full and informed discussion with the parents. In most cases, parental and patient counseling should begin as soon as possible.

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Evaluation and Management of Disorders of Sex Development: Multidisciplinary Approach to a Complex Diagnosis

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Page 1601

In 2006, a task force sponsored by the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society proposed a new nomenclature and classification system as well as new management recommendations for DSD (7). [...] This new terminology has replaced the older terms *hermaphroditism* and *pseudohermaphroditism* and emphasizes the genetic origin of the disorders (2) (Table 1).

Page 1603

At transverse US, female genitalia in the early second trimester appear as three parallel lines in the expected location between the fetal legs (Fig 3). During later gestation, the female genitalia appear as three bumps with the clitoris directed caudally in the midline. In the male, a small semicircular structure representing the scrotal sac is observed in the early second trimester, with the penis directed anteriorly and superiorly in the midline. From the late second trimester onward, the testes can be seen within the scrotum (9) (Fig 4). Errors in diagnosis may occur if the fetal legs are adducted or if the US beam is directed at the wrong angle (Fig 5).

Page 1609

Voiding cystourethrography and genitography are useful in defining the internal anatomy of the urethra, vagina, cervix, and urethrovaginal confluence. All perineal orifices should be examined.

Page 1612

The following factors play a crucial role in the complex process of sex assignment: diagnosis, karyotype, appearance of the external genitalia, type of gonads present, need for surgical interventions to provide consistency with the sex of rearing, use of hormonal therapy, potential for fertility, parental wishes, and parental cultural beliefs.

Page 1615

Gonadoblastomas are the most common tumors arising from intraabdominal or intrapelvic gonads, with a 25% rate of occurrence (40). These tumors are considered precursors to malignant seminomas and nonseminomatous germ cell tumors. On US images, an echogenic focus associated with the pelvic organs or in an ectopic gonad or labioscrotal fold should be investigated, as gonadoblastomas are often calcified. They may appear as solid tumors on CT or MR images and may be associated with hemorrhagic ascites (Fig 17).