Ambiguous Genitalia: Evaluation and Management in the Newborn

Bonnie McCann-Crosby, MD*

*Division of Pediatric Endocrinology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX.

Educational Gaps

1. Knowing the differential diagnosis of ambiguous genitalia in the neonate will lead to more appropriate diagnostic evaluation and timely management.

2. The evaluation of patients with disorders of sexual development requires an experienced multidisciplinary team.

Abstract

Infants born with ambiguous genitalia pose challenges to medical providers and can cause parental anxiety and distress. Disorders of sexual development (DSD) are classified into 3 major categories (46,XY DSD, 46,XX DSD, and sex chromosome DSD). A thorough history, physical examination, and appropriate diagnostic testing are needed to identify the underlying etiology. An understanding of normal sexual development can help clinicians tailor their initial diagnostic evaluation for an infant with ambiguous genitalia. The involvement of a multidisciplinary team that is experienced in DSD is essential. Sex assignment should be made only after all diagnostic evaluations have been considered; families should be an integral part of the decision-making process.

Objectives

After completing this article, readers should be able to:

1. Describe the normal process of sexual development for male and female infants.

2. Understand the 3 major categories of DSD (XY DSD, XX DSD, sex chromosome DSD).

3. Explain which clinical findings are consistent with ambiguous genitalia and when further evaluation is needed.

4. Determine the appropriate initial diagnostic approach for an infant born with ambiguous genitalia.

AUTHOR DISCLOSURE

Dr McCann-Crosby has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.
INTRODUCTION
Infants whose genitalia cannot clearly be classified as either a male or female phenotype are considered to have a disorder of sexual development (DSD). Evaluating a newborn with ambiguous genitalia can be challenging and requires prompt investigation to determine the underlying cause. A multidisciplinary team approach including neonatology, endocrinology, gynecology, urology, genetics, ethics, social work, and psychology is recommended when evaluating infants with ambiguous genitalia. Parents should always be included in discussions about evaluation and management, and they should be key stakeholders in the sex-assignment decision.

DSD can be classified into 3 broad categories: 46,XX DSD, 46,XY DSD, and sex chromosome DSD. A systematic approach in the evaluation of ambiguous genitalia can help discover the underlying etiology in many cases, but an etiology may not be identified. This article focuses on the process of normal sexual development and describes the clinical evaluation and treatment of newborns with ambiguous genitalia.

NORMAL SEXUAL DIFFERENTIATION
During early embryogenesis, the gonads and internal structures of male and female fetuses are phenotypically identical and bipotential. The bipotential gonad differentiates into either an ovary or a testis, depending on specific gene expression. The first step in male sex development is expression of the sex-determining region on the Y chromosome (SRY), which occurs around the sixth week of gestation. SRY triggers further sex-determining genes and transcription factors that are necessary for maturation and differentiation of cell types in the testis, including Sertoli and Leydig cells. Around the eighth week of gestation, the primitive testes begin to produce hormones. Production of testosterone by the Leydig cells leads to development of the wolffian ducts into male internal genitalia (epididymis, vas deferens, and seminiferous tubules). Production of anti-müllerian hormone (AMH) by the Sertoli cells leads to involution of the müllerian ducts into female internal ducts. The development of the external male genitalia (epididymis, vas deferens, and seminal vesicles) requires prompt investigation to determine the underlying cause. A multidisciplinary team approach including neonatology, endocrinology, gynecology, urology, genetics, ethics, social work, and psychology is recommended when evaluating infants with ambiguous genitalia. Parents should always be included in discussions about evaluation and management, and they should be key stakeholders in the sex-assignment decision.

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46,XX DSD
46,XX DSDs can be subdivided into either disorders of androgen excess or disorders of ovarian development. These conditions are summarized in Table 1.

The most common cause of genital ambiguity in a 46,XX female is congenital adrenal hyperplasia (CAH). CAH is an autosomal recessive condition with a defect in the synthesis of cortisol. The most common cause of CAH is 21-hydroxylase deficiency, which accounts for 95% of cases; however, 11β-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase (HSD) deficiency can also cause virilization of a female infant. The block in the production of cortisol leads to shunting of cortisol precursors toward the androgen pathway, which leads to virilization of the external genitalia. 46,XX individuals with CAH have normal female internal genital development. Females born with CAH can present with a wide range of genital ambiguity, from mild clitoromegaly to phenotypic-appearing males with empty scrotal sacs. Figure 1 shows a severely virilized female infant with 21-hydroxylase deficiency. Infants with classic 21-hydroxylase deficiency also have deficient aldosterone production and can present with a salt-wasting crisis (hyponatremia, hyperkalemia, hypoglycemia, hypovolemia, shock). All states now have newborn screening programs that measure 17-hydroxyprogesterone levels, which are elevated in cases of 21-hydroxylase deficiency.

Aromatase deficiency is a condition in which patients are unable to convert androgen precursors to estrogen. Aromatase deficiency in the placenta leads to virilization of both the mother and the fetus. Maternal causes of androgen excess that can lead to virilization of a 46,XX infant include ingestion of androgens or progestins, virilizing adrenocortical tumors, ovarian tumors, or luteomas.

Disorders of ovarian development in a 46,XX individual that can present with ambiguous genitalia include ovotesticular DSD and 46,XX testicular DSD. In ovotesticular DSD, the gonad contains both ovarian and testicular tissue. Patients with ovotesticular DSD can present with a spectrum of genital ambiguity as well as both male and female internal duct structures. In 46,XX testicular DSD, both of the gonads develop into testes, and these patients do not have ovarian or müllerian components. These patients can present with mild genital abnormalities including internal female genitalia (uterus, fallopian tubes, and upper one-third of the vagina), and the wolffian ducts regress. Without testosterone and DHT, the genital tubercle will form the clitoris, the urethral folds become the labia minora, and the labioscrotal swellings become the labia majora, leading to a female external phenotype.
hypospadias and undescended testes, though in many cases they are phenotypically normal males who present later in life because of infertility.

46,XY DSD

46,XY DSDs can be classified further into disorders of testicular development and disorders of androgen synthesis or action. These conditions are summarized in Table 2.

Disorders of testicular development include gonadal dysgenesis, gonadal regression or vanishing testes syndrome, and XY ovotesticular DSD. In 46,XY complete gonadal dysgenesis (Swyer syndrome), no testicular development occurs and patients appear as phenotypic females with bilateral streak gonads and normal müllerian structures. Patients with 46,XY partial gonadal dysgenesis have some degree of testicular development and can present with variable internal and external phenotypes depending on how functional the testes are. Several syndromes, including camptomelic dysplasia, Frasier syndrome, and Denys-Drash syndrome, are associated with XY gonadal dysgenesis.

Figure 1. A 46,XX female infant with severe virilization caused by salt wasting congenital adrenal hyperplasia because of 21-hydroxylase deficiency. Figure shows significant clitoromegaly, fusion of the labioscrotal folds with hyperpigmentation, no palpable gonads, single urethral meatus. The infant is at Prader stage V.
Vanishing testes or testicular regression syndrome is a condition in which testes are absent in a 46,XY individual. These individuals are thought to have disappearance or regression of the testes in utero after an insult such as torsion or vascular thrombosis. The appearance of the external genitalia depends on the timing of the testicular regression in relation to sexual development: testicular regression before 8 weeks of gestation results in a phenotypic female, loss between 8 and 10 weeks results in ambiguous genitalia, and loss after 12 weeks will result in normal male external genitalia.

XY ovotesticular DSD is a condition in which an XY individual has both ovarian and testicular tissue. Patients with XY ovotesticular DSD most commonly present with ambiguous genitalia or severe hypospadias.

Disorders of androgen action include complete or partial androgen insensitivity. These conditions result from mutations in the androgen receptor gene. The phenotype of patients with androgen insensitivity depends on the degree of tissue responsiveness to androgen activity. Patients with complete androgen insensitivity have female external genitalia with a blind vaginal pouch. These individuals typically present in adolescence with primary amenorrhea, though in some instances they are identified earlier because of inguinal or labial swellings containing testes. Patients with partial androgen insensitivity can present with a wide range of phenotypes, from ambiguous genitalia to phenotypic males who present with infertility in adulthood.

Disorders of androgen synthesis include testosterone biosynthesis enzyme defects, Leydig cell hypoplasia/aplasia, and 5α-reductase deficiency. Enzymatic defects in the adrenal gland or testes can lead to decreased production of testosterone and cause undervirilization in 46,XY individuals. The adrenal biosynthesis pathway is shown in Fig 2.

**Table 2. 46,XY Disorders of Sexual Development (DSD) That Can Present With Ambiguous Genitalia**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CLINICAL FEATURES</th>
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<tbody>
<tr>
<td>Disorders of testicular development</td>
<td></td>
</tr>
<tr>
<td>• Gonadal dysgenesis</td>
<td>Wide range of undervirilization depending on degree of dysgenesis</td>
</tr>
<tr>
<td>• Gonadal regression/Vanishing testes</td>
<td>Wide range of undervirilization depending on the timing of gonadal regression in utero</td>
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<tr>
<td>• XY ovotesticular DSD</td>
<td>Typically present with ambiguous genitalia or severe hypospadias</td>
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<tr>
<td>Disorders of androgen action</td>
<td></td>
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<tr>
<td>• Androgen insensitivity syndrome</td>
<td>Wide range of phenotypes depending on the degree of tissue responsiveness to androgens</td>
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<tr>
<td>Disorders of androgen synthesis</td>
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<tr>
<td>• Testosterone biosynthesis enzyme defects</td>
<td>Wide range of undervirilization/ambiguity depending on the specific enzyme deficiency</td>
</tr>
<tr>
<td>7-dehydrocholesterol reductase deficiency</td>
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<tr>
<td>STAR protein/P450scc deficiency</td>
<td>Can present with salt-wasting crisis depending on the specific enzyme defect</td>
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<tr>
<td>3β-HSD type 2 deficiency</td>
<td></td>
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<tr>
<td>17α-hydroxylase/17,20 lyase deficiency</td>
<td></td>
</tr>
<tr>
<td>17β-hydroxysteroid dehydrogenase type 3 deficiency</td>
<td></td>
</tr>
<tr>
<td>• Leydig cell hypoplasia/aplasia</td>
<td>Undervirilization depends on degree of Leydig cell hypoplasia</td>
</tr>
<tr>
<td>• 5α-reductase deficiency</td>
<td>Ambiguous genitalia, micropenis, hypospadias; spontaneous virilization can occur at puberty</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>• Hypogonadotropic hypogonadism</td>
<td>Can present with micropenis and other pituitary hormone deficiencies</td>
</tr>
</tbody>
</table>

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Disorders of androgen synthesis include testosterone biosynthesis enzyme defects, Leydig cell aplasia or hypoplasia, and 5α-reductase deficiency. Enzymatic defects in the adrenal gland or testes can lead to decreased production of testosterone and cause undervirilization in 46,XY individuals. The adrenal biosynthesis pathway is shown in Fig 2. As shown in the figure, the synthesis of testosterone begins...
with cholesterol. Deficiency of 7-dehydrocholesterol reductase results in impaired synthesis of cholesterol and leads to Smith-Lemli-Opitz syndrome. This syndrome is characterized by variable clinical features including cardiac defects, cleft palate, syndactyly, polydactyly, and genital ambiguity. The conversion of cholesterol to pregnenolone depends on the steroidogenic acute regulatory (StAR) protein and P450scc; hence, defects in these 2 enzymes can lead to undervirilized males. These patients typically appear as phenotypic females with undescended testes. Individuals with StAR mutations have adrenal insufficiency and lipid accumulation and enlargement of their adrenal glands. Patients with P450scc have a phenotype similar to that of individuals with StAR deficiency. 3β-HSD type II is the enzyme that converts dehydroepiandrosterone to androstenedione. Deficiencies in 3β-HSD type II can cause hypospadias, microopenis, or more severe undervirilization/ambiguity in addition to cortisol and mineralocorticoid deficiency. Mutations in the CYP17 gene can lead to deficiency in the activities of 17α-hydroxylase and 17,20 lyase. XY individuals with 17α-hydroxylase/17,20 lyase deficiency can present with varying degrees of undervirilization.

Figure 2. Adrenal biosynthesis pathway.
ranging from micropenis, perineal hypospadias, and cryptorchidism to a complete female external phenotype. 17β-HSD type III deficiency leads to an inability to convert androstenedione to testosterone. These XY individuals can have either a female or ambiguous external phenotype. Mutations in the luteinizing hormone (LH)/human chorionic gonadotropin (hCG) receptor can lead to testicular Leydig cell aplasia or hypoplasia. Without normal production of testosterone by the Leydig cells, undervirilization of the XY male will occur. The extent of undervirilization depends on the degree of Leydig cell hypoplasia.

5α-reductase deficiency leads to a defect in the conversion of testosterone to DHT. Without adequate levels of DHT to virilize the external genitalia, XY individuals can present with ambiguous genitalia, micropenis, hypospadias, or female external genitalia. These patients can have spontaneous virilization during puberty because of the increased testosterone levels.

**SEX CHROMOSOME DSD**

Sex chromosome DSD includes Turner syndrome (45,X), Klinefelter syndrome (47,XXY), and mosaic karyotypes (e.g., 45,X/46,XY; 46,XX/46,XY). Patients with nonmosaic Turner syndrome and Klinefelter syndrome do not present with ambiguous genitalia, whereas those with the mosaic karyotypes such as 45,X/46,XY can present with varying degrees of genital ambiguity depending on how developed and functional the testes are.

**DIAGNOSTIC EVALUATION**

Clinical features that raise suspicion of a DSD include apparent female genitalia with clitoromegaly, inguinal or labial mass, or posterior labial fusion; micropenis with bilateral nonpalpable testes, hypospadias with undescended testes, isolated penoscrotal, or perineoscrotal hypospadias; or a discordance between prenatal karyotype and genital appearance. Clitoromegaly is defined as a clitoral length greater than 9 mm or clitoral width greater than 6 mm in a full-term infant. A stretched penile length that is ~2.5 SD below the mean for age is considered to be a micropenis.

The evaluation of a newborn with ambiguous genitalia requires a thorough history, physical examination, laboratory testing, and imaging studies. Parents should be asked about consanguinity, which may indicate an increased risk of autosomal recessive disorders, such as CAH. A history of unexplained infant deaths in the family can also be concerning for undiagnosed salt-wasting CAH. A family history of ambiguous genitalia, urologic anomalies, or female infertility/amenorrhea should also be obtained. Mothers should be asked about the use of any drugs or exposure to environmental factors that could lead to virilization of a female infant. Maternal virilization should be noted because it could suggest a maternal tumor that produced excess androgen. Results of any prenatal tests, including ultrasonography and karyotyping, should be obtained.

The physical examination should begin with a general assessment. As mentioned previously, some syndromes are associated with genital ambiguity and have characteristic physical features. Any dysmorphic features or malformations should be noted because they may suggest an underlying genetic disorder. Midline defects can be associated with hypothalamic-pituitary abnormalities and can cause hypogonadotropic hypogonadism. Hypertension and dehydration can be associated with some forms of CAH, so it is important to evaluate hydration status and blood pressure. Jaundice may be a sign of cortisol deficiency or hypopituitarism. The examination of the external genitalia should include the development of the genital tubercle, which forms the penis in males and the clitoris in females. The degree of fusion of the labioscrotal folds should be noted, as should the texture and pigmentation of the genital skin. It is important to palpate the labioscrotal folds and inguinal regions bilaterally for the presence of gonads. A palpable external gonad will be either a testes or an ovotestes. The size and location of the gonads should be documented. A stretched phallic length and width should be measured, and the presence or absence of chordee should be noted.

The location of the urethral opening or urogenital sinus should be determined (are there separate vaginal and urethral openings, or is there a common channel?). The degree of hypospadias should be documented if present (is the urethral opening proximal/perineal, mid-shaft, or distal/glandular on the ventral surface of the phallic structure?). In contrast to hypospadias, epispadias is the opening of the urethral or urogenital sinus on the dorsal surface of the phallic structure. Epispadias is a rare occurrence and can be part of a spectrum of conditions in which there is failure of fusion of abdominal or pelvic organs, including the external genitalia.

All patients with ambiguous genitalia or a question of sex assignment require a routine chromosome analysis as initial investigation. It should be obtained within the first 24 hours after birth, and the laboratory should be notified to expedite the results. A chromosomal microarray analysis is recommended to look for small deletions or duplications that may not be identified on routine karyotype. For patients with ambiguous genitalia and nonpalpable gonads, there should be a high suspicion of CAH. Initial evaluation should include measurement of serum electrolytes to look for salt wasting, serum glucose that may be low in cases of cortisol...
deficiency, and 17-hydroxyprogesterone to evaluate for 21-
hydroxylase deficiency. A corticotropin (ACTH)-stimulation
test may be necessary to evaluate the cortisol response
and enzymatic deficiencies that can cause CAH. It can be
done by obtaining baseline and ACTH-stimulated levels of
cortisol, 17-hydroxyprogesterone, 17-hydroxypregnenolone,
progesterone, androstenedione, dehydroepiandrosterone, de-
oxycorticosterone, 11-deoxycortisol, and testosterone. The
ACTH-stimulation test should not delay treatment in cases
of suspected CAH. In any suspected case of CAH, renin and
aldosterone levels also should be obtained.

Additional testing includes baseline gonadotropins (LH
and follicle-stimulating hormone), which may be low in
cases of hypogonadotropic hypogonadism and indicative of
possible pituitary deficiency. Hypogonadotropic hypogonad-
ism can be a cause of micropenis in 46,XY individuals. An
AMH level is a reliable marker of the presence and function
of testicular tissue and can be helpful in evaluating under-
virilized XY individuals. AMH levels will be low in cases of
vanishing testes, XY gonadal dysgenesis, or persistent müll-
erian duct syndrome. AMH levels can be elevated in cases
of androgen insensitivity and hypogonadotropic hypogon-
adism. An hCG-stimulation test is used to evaluate the production of testosterone from testicular tissue. The
hCG-stimulation test requires measuring baseline and stim-
ulated levels of testosterone and DHT. The ratio of testos-
erone to DHT will be elevated in cases of 5α-reductase
deficiency. An inadequate response to hCG stimulation in
an XY individual can be indicative of gonadal dysgenesis,
ovotesticular DSD, LH receptor defect, or hypogonadotropic
hypogonadism. High testosterone levels in an undervirili-
lized 46,XY patient should raise suspicion for androgen
insensitivity, and genetic testing should be considered.

The internal anatomy of any patient with ambiguous
genitalia should be evaluated with pelvic/abdominal ultra-
sonography or magnetic resonance imaging. Imaging can
identify the presence or absence of müllerian structures
(uterus) and the location of gonadal tissue. Gonadal biopsy
may be necessary to determine the type of gonadal tissue in
cases of suspected ovotesticular DSD or gonadal dysgenesis.

MANAGEMENT

The uncertainty of an infant’s gender is stressful and
upsetting to families. The prompt involvement of a
multidisciplinary team that is knowledgeable in DSD is
essential when evaluating these patients. This team should
include endocrinology, urology, gynecology, genetics, psy-
chology, social work, and ethics. Ruling out life-threatening
emergencies such as CAH should be the initial priority. The
parents should be involved in all discussions regarding sex
assignment and should be updated on testing results as they
become available. Although parents are eager to tell friends
and family the sex of their newborn, it is important that
careful consideration and thorough evaluation are complete
before a sex assignment decision is made. Before making
the final sex assignment, it is important to use gender-
neutral terms when discussing the infant such as “baby”
instead of using “she” or “he.” It is recommended that
parents meet with a psychologist who can help them with
coping techniques and provide guidance on how to talk to
friends and family about their newborn. Many factors,
including phenotypic sex (appearance of the external
and internal genitalia), genotypic sex (karyotype), hor-
monal sex (hormonal profile: testosterone, DHT, adrenal
steroid profile), reproductive sex (potential to have biolog-
ical children), and parental perception, influence sex
assignment. Discussing each of these components of
sexual development with the family can help demystify
the process and reduce anxiety for families as they partic-
ipate in the sex assignment process.

Surgical intervention (gonadoplasty, vaginoplasty, gonad-
ectomy) must be delayed until a clear diagnosis is estab-
lished and should be performed only by an experienced
surgeon. The benefits of any surgical or medical procedure
must clearly outweigh the risks, and any unnecessary
procedures should be delayed until the child is old enough to
make an informed decision.

Once a sex-assignment decision is made, the child and
family will need long-term follow-up with medical providers
who are experienced with DSD. Ongoing education is
essential, because many of these patients will require sur-
gery and hormonal therapy. It is important to assess the
patient’s and parents’ satisfaction with the sex-assignment
decision. Psychological assessment at regular intervals is
recommended to screen for mental health issues such as
gender dysphoria and to provide support for families.

CONCLUSIONS

The finding of ambiguous genitalia in the newborn can be
distressing to both health-care providers and families. A
thorough, stepwise approach to diagnosis that involves a
multidisciplinary team is necessary. Each case of ambig-
uous genitalia is unique, and a basic understanding of the
differential diagnosis of DSD can help guide the evaluation
of these newborns. Open communication between the
medical team and the families is important, and the families
must be involved in all decisions about sex assignment and
surgical management.
ACKNOWLEDGMENT

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Suggested Reading

Ahmed SF, Rodie M. Investigation and initial management of ambiguous genitalia. Best Pract Res Clin Endocrinol Metab. 2010;24(2):197–218


American Board of Pediatrics Neonatal–Perinatal Content Specifications

- Know normal fetal sexual differentiation.
- Differentiate among disorders of testicular hormone synthesis or action.
- Know the etiology of abnormal sexual differentiation.
- Know the diagnostic approaches to and management of abnormal sexual differentiation.
- Know the etiology of and diagnostic approaches to an infant with ambiguous genitalia, not including congenital adrenal hyperplasia.
- Know how to evaluate and manage an infant with micropenis.
- Know how to evaluate and manage an infant with hypospadias and epispadias.

Parent Resources from the AAP at HealthyChildren.org

- English only: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Explaining-Disorders-of-Sex-Development-Intersexuality.aspx
1. A pregnant woman is being evaluated at a prenatal visit at 20 weeks’ gestation and undergoes routine ultrasonography. The infant is noted to have evidence of male genitalia. Which of the following statements regarding sexual differentiation in the fetus is correct?
   A. The normal 46,XY fetus starts to have a specific male gonadal structure destined to become the testes at the 2-cell embryonic stage that is visible on electron microscopy.
   B. The expression of the sex-determining region on the Y chromosome occurs at the 16th week of gestation.
   C. Production of testosterone by the Sertoli cells leads to increased proliferation of testicular cells.
   D. The Leydig cells produce anti-müllerian cells that cause inhibition of uterine growth.
   E. The development of the external male genitalia depends on the activity of dihydrotestosterone, which is converted from testosterone by the enzyme 5α-reductase.

2. A newborn infant is noted to have ambiguous genitalia. Consultation is obtained and evaluation is initiated including an immediate karyotype test, which shows the karyotype to be 46,XX. Which of the following conditions is the most common cause of genital ambiguity in a 46,XX female?
   A. Androgen insensitivity.
   B. Adrenocortical tumor.
   C. Congenital adrenal hyperplasia.
   D. Aromatase deficiency.
   E. Ovotesticular dysgenesis.

3. A newborn infant who is being evaluated for ambiguous genitalia is noted to have 46,XY karyotype. The patient is noted to have a cleft palate and polydactyly. Further testing reveals deficiency of 7-dehydrocholesterol reductase. Which of the following conditions does this infant have?
   A. Partial androgen insensitivity.
   B. XY ovotesticular disorder of sexual differentiation.
   C. Pregnenolone synthase deficiency.
   D. Smith-Lemli-Opitz syndrome.
   E. Mosaic Kleinfelter/Turner syndrome.

4. While taking the history of a patient with ambiguous genitalia, it is revealed that the mother and father are first cousins and that there is a history of unexplained infant deaths in the family. Which of the following conditions should be suspected?
   A. Severe androgen insensitivity syndrome.
   B. Salt-wasting congenital adrenal hyperplasia.
   C. Ovotesticular carcinoma.
   D. Wolffian duct obstruction.
   E. Leydig cell hyperplasia.

5. A newborn infant is transferred to a children’s hospital soon after birth for evaluation of ambiguous genitalia. Which of the following actions is appropriate?
   A. Even if there is uncertainty, a sex should be assigned to the newborn within the first day to reduce parental anxiety, as well as for legal purposes.
   B. The main reason for transfer to a children’s hospital is that optimal results are obtained when surgical intervention occurs in the first few days after birth to inhibit further disordered development, regardless of the etiology.

NOTE: Learners can take NeoReviews quizzes and claim credit online only at: http://neoreviews.org.
C. A chromosome analysis should be obtained within the first 24 hours after birth, and the laboratory notified to expedite the results.

D. In cases with suspicion or evidence of cortisol deficiency, treatment should not be given until the results of a corticotropin-stimulation test are obtained.

E. The optimal imaging choice in this situation to evaluate gonadal tissue is a noncontrast computed tomography scan.
are seen, usually in consanguineous families. Mutations of transcription factors HESX1, SOX2, and SOX3 have been reported in patients with SOD. (5)

Management
The mainstay of treatment is replacement with appropriate hormones. Neonates diagnosed with congenital hypopituitarism require monitoring for evolving hormone deficiencies. Life-long follow-up by a multidisciplinary team aims to address the complex needs of those patients, including periodic visual and auditory assessments and neurodevelopmental support. Genetic counseling should be offered in cases in which a genetic defect has been detected.

Clinical Course of the Index Newborn
The infant started receiving thyroid hormone supplementation and stress dose steroids, leading to normalization of his glucose levels and symptom resolution. He also started receiving human growth hormone supplementation, and received a dose of testosterone in hopes of phallus size normalization. He was diagnosed with bilateral mild high-frequency sensorineural hearing loss, but has been meeting developmental milestones up to this point.

Lessons for the Clinician
- Persistent, clinically symptomatic hypoglycemia can be a sign of a serious endocrine disorder requiring specific treatment beyond maintenance intravenous glucose.
- Use of critical hypoglycemia laboratory values for neonates, paired with careful evaluation of clinical findings, including penile size and dysmorphic features, allow for timely identification of the source of hypoglycemia and narrowing of the differential diagnosis.
- Brain magnetic resonance imaging is an important diagnostic tool in neonates with hypopituitarism, allowing identification of structural brain anomalies suggestive of septo-optic dysplasia.

References

Correction
An error was noted in the March 2016 article “Ambiguous Genitalia: Evaluation and Management in the Newborn” (McCann-Crosby. NeoReviews. 2016;17(3):e144. DOI: 10.1542/neo.17-3-e144). Under the heading 46,XX DSD, in the second paragraph, the word “hypokalemia” should read “hyperkalemia.”

The correct sentence should read: “Infants with classic 21-hydroxylase deficiency also have deficient aldosterone production and can present with a salt-wasting crisis (hyponatremia, hyperkalemia, hypoglycemia, hypovolemia, shock).”

The article has been corrected and resupplied online. The journal regrets the error.
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/17/3/e144

An erratum has been published regarding this article. Please see the attached page for:
http://neoreviews.aappublications.org/content/17/4/e222.full.pdf

Data Supplement at:
http://neoreviews.aappublications.org/content/suppl/2016/03/03/17.3.e144.DC1