Ambiguous Genitalia

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IMPORTANT POINTS

1. Wolffian ducts are the male primordial tissue; müllerian ducts are the female primordial tissue.
2. Male pseudohermaphroditism is due to undervirilization of the genitalia; female pseudohermaphroditism is due to virilization of the genitalia.
3. The vast majority of infants who have ambiguous genitalia will be chromosomal females with 21-hydroxylase deficiency.
4. The presence of palpable gonads indicates that the neonate is a chromosomal male.
5. The scrotum is formed by fusion of the labioscrotal folds *only* during the first trimester.

Introduction

The newborn whose genitalia are ambiguous presents a diagnostic challenge to the physician and an emotional crisis for the family. Families are anxious about the sex of their child, and societal pressure for gender identification is great. Lingering doubts of gender identity may affect the parent-infant relationship significantly. Evaluation and diagnosis must proceed rapidly to determine the sex of rearing and to initiate necessary medical interventions. From the moment a child who has ambiguous genitalia is born, consultation with the pediatrician, pediatric endocrinologist, geneticist, and surgeon should ensue. Frequent updates, together with psychological support, should be provided to the family as more information becomes available.

Ambiguous genitalia is due to undermasculinization of genetic males or virilization of genetic females. Four broad categories of disorders of sexual differentiation are responsible for the development of ambiguous genitalia. In males, the problem usually can be attributed to testicular synthetic defects in male sex hormone (androgen) biosynthesis or resistance to those hormones in the target tissues (male pseudohermaphroditism). In females, the most common cause of ambiguous genitalia is a form of congenital adrenal hyperplasia (CAH), 21-hydroxylase deficiency, an adrenal enzyme defect that leads to excess androgens (female pseudohermaphroditism). True hermaphroditism, a condition in which both ovarian and testicular tissue are found in either the same or opposite gonads of the same individual, may include ambiguous genitalia and both müllerian and wolffian internal structures. 46,XX karyotype is the most common karyotype found in true hermaphroditism. Finally, incomplete gonadal dysgenesis, a condition that involves partial testis determination in the presence of a Y chromosome, may have varying degrees of ambiguity. We will focus primarily on male and female pseudohermaphroditism.

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Normal Sexual Differentiation

Critical to understanding ambiguous genitalia and to determining the sex of rearing is a basic knowledge of sexual differentiation. The innate tendency of the bipotential fetus is to develop as a female. Without influence from a cascade of events initiated by the testes-determining factor, now known as the sex determining region of the Y chromosome (SRY), the internal and external genitalia will be female. Complete newborn male differentiation and development requires: 1) the action of the SRY and downstream genes, 2) testicular production of both anti-müllerian hormone (AMH), also called müllerian inhibiting substance (MIS), and testosterone, 3) normal gonadotropin production by the hypothalamic-pituitary axis (during the second and third trimester), 4) conversion of testosterone to dihydrotestosterone (DHT) by 5 α-reductase, and 5) end organ response to androgens.

The bipotential gonad in humans begins its development close to the mesonephros (primitive kidney). By approximately day 42 of gestation, the germ cells that originate in the yolk sac endoderm migrate into the gonadal ridge; the bipotential gonad then is formed from three sources: mesodermal cells of the coelomic epithelium, mesodermal cells from the underlying mesenchyma, and germ cells originating in the yolk sack or endoderm. The primordial germ cells are the progenitors of the spermatogonia of the testis and the oocyte of the ovary. The mesodermal cells from the coelomic epithelium form the Sertoli cells in the male and the granulosa cells in the female, while the mesenchyma gives rise to the Leydig cells in the male and the theca and stroma cells in the female. The Sertoli (AMH-producing) and Leydig (testosterone-producing) cells are found in the testis; granulosa and theca cells are found in the ovary. By day 43 to 50 of gestation, the bipotential gonad differentiates into a testis in the presence

ABBREVIATIONS

ACTH:	Adrenocortical trophic hormone
AMH:	Anti-müllerian hormone
CAH:	Congenital adrenal hyperplasia
DHEA:	Dehydroepiandrosterone
DHT:	Dihydrotestosterone
hCG:	Human chorionic gonadotropin
MIS:	Müllerian inhibiting substance
SRY:	Sex-determining region of the Y chromosome
17-OHP:	17 α-hydroxyprogesterone

of SRY; in its absence, an ovary is formed. The SRY gene product (a transcription factor) binds to specific DNA sequences that regulate transcription of other genes affecting testicular differentiation.

By day 43 to 50 of gestation, the developing fetus contains both female (müllerian) and male (wolffian) genital ducts, making chromosomal male and female fetuses phenotypically indistinguishable. The müllerian ducts have the potential to develop into fallopian tubes, uterus, and the upper one third of the vagina; wolffian ducts differentiate into the vas deferens, epididymis, and seminal vesicles (Fig. 1). Testicular secretion of AMH (first postulated by Jost in 1947) leads to regression of the female müllerian structures, and secretion of testosterone leads to full differentiation and stabilization of the male internal and external genitalia. First trimester testicular testosterone production is primarily under the control of placentally derived human chorionic gonadotropin (hCG); fetal pituitary gonadotropins play a central role in the second and third trimesters. Testosterone is converted by 5 α-reductase in the genital skin to its more active metabolite DHT, which is responsible for forming the scrotum and penis from the labioscrotal and urethral folds by the end of the first trimester (Fig. 2). Fusion of the labioscrotal folds to form a scrotum occurs *only* during the critical first trimester.

In the female fetus, because there is no AMH, the müllerian ducts complete their development; the wolffian genital ducts undergo involution. In the absence of DHT, the labioscrotal folds do not fuse and the clitoris does not enlarge.

Even in the absence of SRY, the presence of two intact X chromosomes is a prerequisite to the formation of normally differentiated ovaries. In fact, X chromosome deletion analysis has demonstrated that deletions on either the long or short arm may lead to abnormal gonadal differentiation, germ cell loss, and oocyte degeneration, ultimately yielding streak gonads (Turner syndrome). Despite the gonadal abnormalities and characteristic phenotypic appearance of patients who have Turner syndrome, the external and internal genitalia are completely normal, demonstrating the critical active role that SRY, AMH, and testosterone play in directing male genital differentiation.

TABLE 1. Descriptive Terms for Ambiguous Genitalia

Bifid scrotum:	Clefting of the scrotum
Clitoromegaly:	Enlargement of the clitoris
Hypospadias:	Opening of the urethra other than at the tip of the penis
Labioscrotal fusion:	Fusion of the labia, yielding a scrotal-like structure
Microphallus:	Full-term male infant who has a stretched phallus less than 2.5 cm
Posterior fusion:	Fusion of the labia at the posterior aspect (closer to the anus)

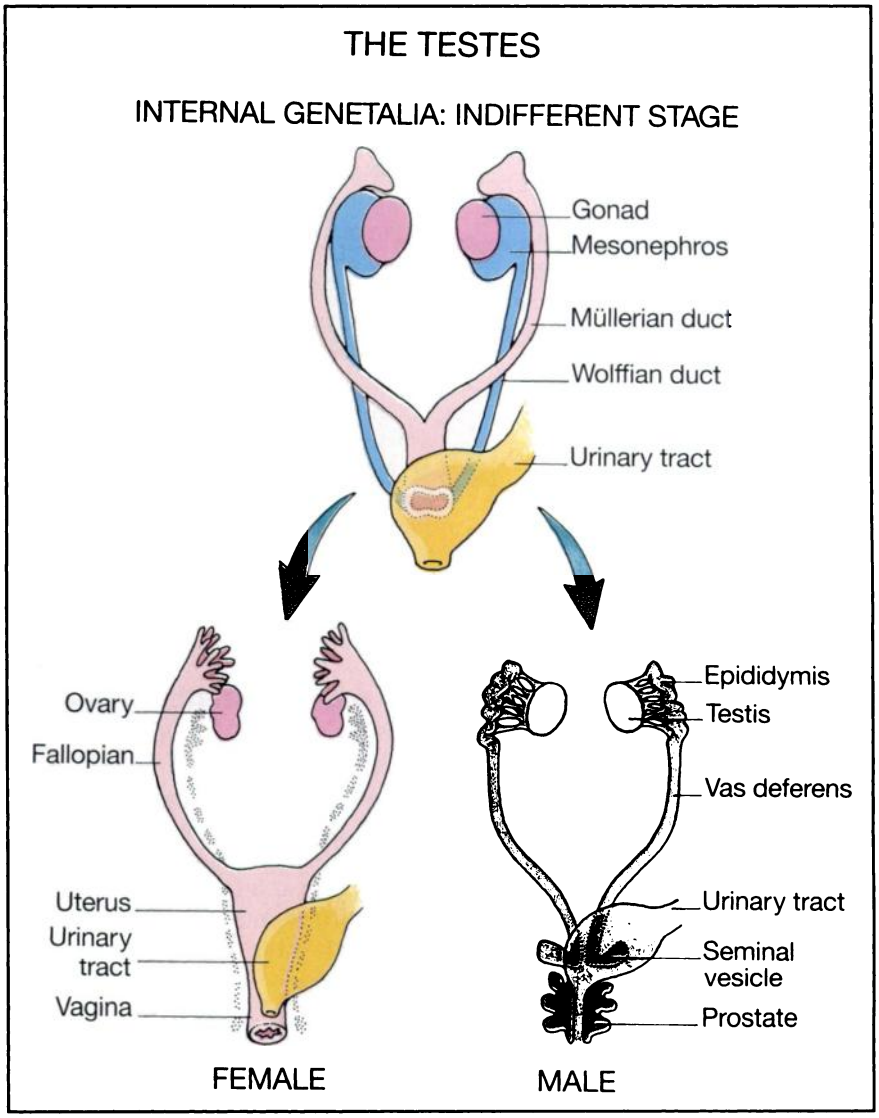

FIGURE 1. Differentiation of internal genitalia.

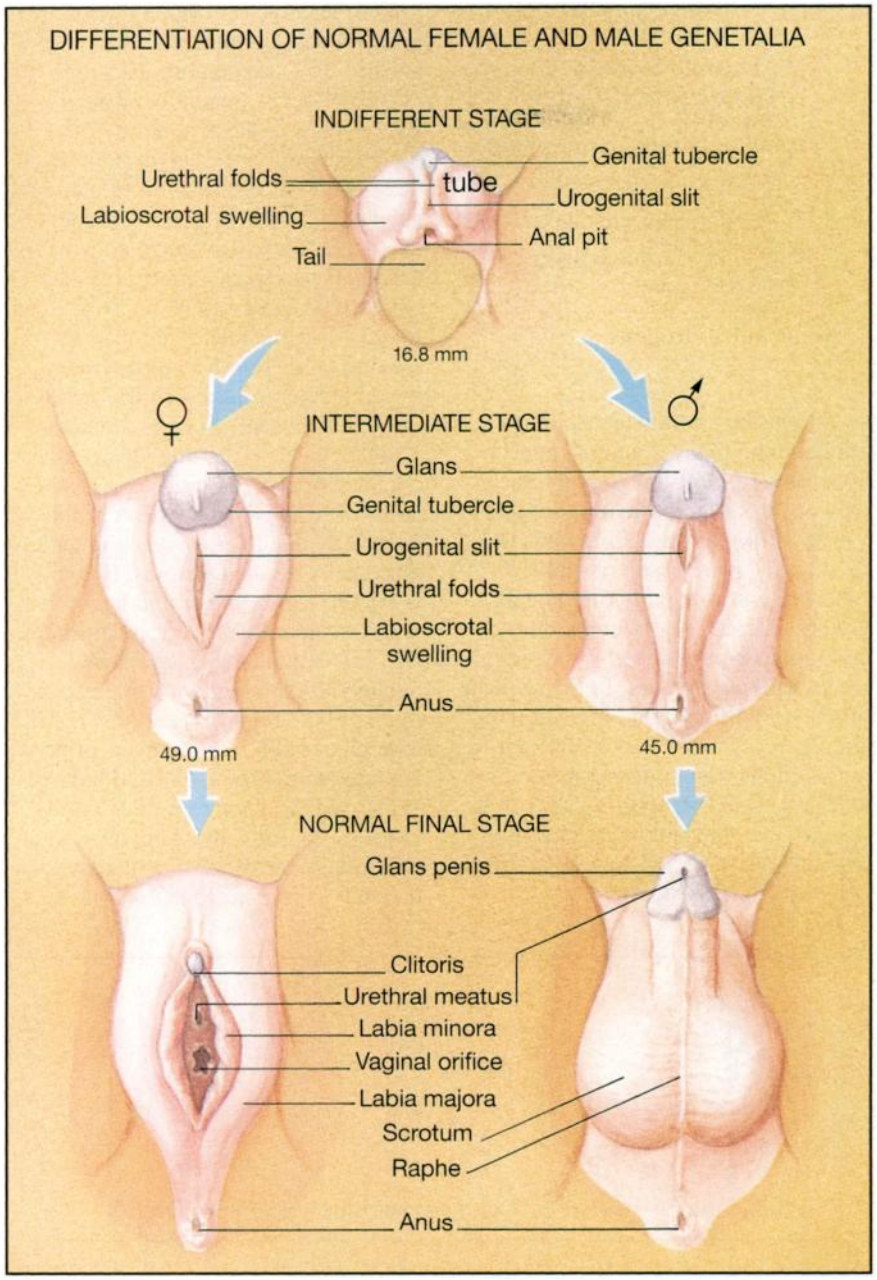

FIGURE 2. Differentiation of external genitalia.

Abnormal Sexual Differentiation: Ambiguous Genitalia

When evaluating a child who has ambiguous genitalia, a thorough family history should be obtained. A child previously affected should raise the possibility of CAH, an autosomal recessive cause of excess adrenal androgens that leads to genital ambiguity. Any neonatal death of a male sibling, who may have escaped immediate diagnosis because androgen excess has no discernible effect on the newborn male external genitalia, strongly suggests CAH with salt loss. Ingestion of progestational agents or the presence of excess androgens in the mother, due to an adrenal tumor or CAH that is poorly controlled, may virilize the female fetus.

CLINICAL EVALUATION

A careful physical examination is essential in the evaluation of the child whose genitalia are ambiguous. An accurate description of the degree of hypospadias, labioscrotal fusion, and stretched phallus length can define ambiguous genitalia, but does not establish a diagnosis. The phenotypic appearance of the external genitalia of the newborn will be influenced markedly by the timing of androgen excess or deficiency. In the female, excess androgen exposure during the first-trimester may cause the labioscrotal folds to fuse and a single urogenital sinus rather than distinct urethral and vaginal openings to form. Excess androgen production after the critical first-trimester no longer will lead to labioscrotal fusion, but will result in clitoromegaly. In the male, inadequate androgen production during the first trimester will lead to incomplete virilization of the external genitalia; inadequate testosterone production later in pregnancy will lead to an isolated microphallus and normal-looking scrotum. Resistance to androgen action also will lead to incomplete virilization of the male external genitalia.

The key diagnostic element of the physical examination is the presence or absence of palpable gonads in the scrotum or inguinal canal. If absent, female pseudohermaphroditism is likely. If gonads are present, the diagnostic evaluation will be directed instead to male pseudohermaphroditism. If gonads are present in the scrotum, they almost surely are testicles, and the infant carries a Y chromosome and a functional SRY.

LABORATORY EVALUATION

The controlling laboratory evaluation is the karyotype for genetic sex determination, which should be obtained as quickly as possible. Because of the high rate of both false-positive and false-negative results, it no longer is justified to perform Barr body analysis for chromosomal sex determination. In our laboratory, sex karyotype results are available within 48 hours, allowing for prompt narrowing of diagnostic possibilities and less reliance on the presence or absence of palpable gonads to make a tentative sex determination. Although the vast majority of infants whose gonads are palpable and who have ambiguous genitalia will be XY males, obviating the need for karyotype determination, karyotype still is recommended when the diagnosis is unclear.

A male child who has isolated hypospadias, cryptorchidism, or microphallus may represent varying degrees of undermasculinization, but he does not have ambiguous genitalia. The diagnostic evaluation in this case will be directed toward inadequate production or responsiveness to testosterone. Testicular descent occurs primarily in the third trimester under the influence of gonadotropin-induced androgen production and other unknown mechanisms. Lack of fetal gonadotropin production during the second and third trimester is not associated with a poorly formed scrotum, but may present instead as isolated cryptorchidism or microphallus. Cryptorchidism is a common disorder of sexual development that generally resolves spontaneously in the majority of infants by 3 months of age. Although the presence of cryptorchidism in a neonate is not synonymous with ambiguous genitalia, it is potentially important as evidence of disordered sexual differentiation. Cryptorchidism frequently occurs in association with more obvious manifestations of ambiguous genitalia and as an aspect of diverse dysmorphic syndromes. However, a consistent, inherent endocrine defect associated with cryptorchidism has not been characterized.

It is important to remember that most patients presenting with ambiguous genitalia at birth are genetic females with virilizing CAH due to 21-hydroxylase deficiency. Despite the odds, extreme caution must be exercised in assigning the sex of rearing until the laboratory results are available. The need for identification of the female infant who has CAH is urgent, because if undiagnosed, she may lose salt, which could lead to death.

Female Pseudohermaphroditism (Table 2)

DIAGNOSIS

Virilized female neonates exhibit a wide range of external genital appearances, from mild clitoromegaly and posterior fusion to complete labioscrotal fusion and urogenital sinus, which can open onto the perineum or on the shaft of the clitoris/phallus. Because no AMH was present during gestation, the internal genitalia are female, with ovaries, uterus, and upper one third of the vagina intact. Any posterior labial fusion (defined as a ratio of the distance from anus to fourchette/anus to base of clitoris >0.5) or clitoromegaly (defined as >1 cm clitoral length) constitutes ambiguous genitalia and is suspicious for a virilizing process. In the absence of a history of maternal ingestion of androgens or CAH, it is likely that most female pseudohermaphrodites will have CAH, primarily 21-hydroxylase deficiency, but occasionally 11 α-hydroxylase or 3-β-hydroxysteroid dehydrogenase deficiency.

TABLE 2.
Female Psuedo-Hermaphroditism

Congenital adrenal hyperplasia
21-hydroxylase deficiency
11α-hydroxylase deficiency
3β-hydroxysteroid dehydrogenase deficiency
Maternal androgens

For the newborn whose gonads are not palpable, we generally obtain only a serum 17 α-hydroxyprogesterone (17-OHP) level at the same time the karyotype is ordered because of the high probability of 21-hydroxylase deficiency. An additional serum aliquot should be frozen, in case subsequent evaluation for rarer adrenal enzyme defects is necessary. A serum 11-desoxycortisol level to rule out 11 α-hydroxylase deficiency should be obtained if there is accompanying hypertension or if the 17-OHP level is normal. We usually take two separate 17-OHP levels if the first level was obtained prior to 24 hours of age, the period when levels may be elevated artificially due to cross-reaction with placentally derived steroids. If levels are in the borderline or nondiagnostic range, an adrenocorticotropic hormone (ACTH)-stimulated level can be obtained (0.036 mg/kg up to a maximum of 0.25 mg synthetic ACTH IM, administered 45 to 60 minutes prior to venipuncture). The ACTH-stimulated values will accentuate the enzyme block by causing adrenal precursors proximal to the block to rise disproportionately (Fig. 3).

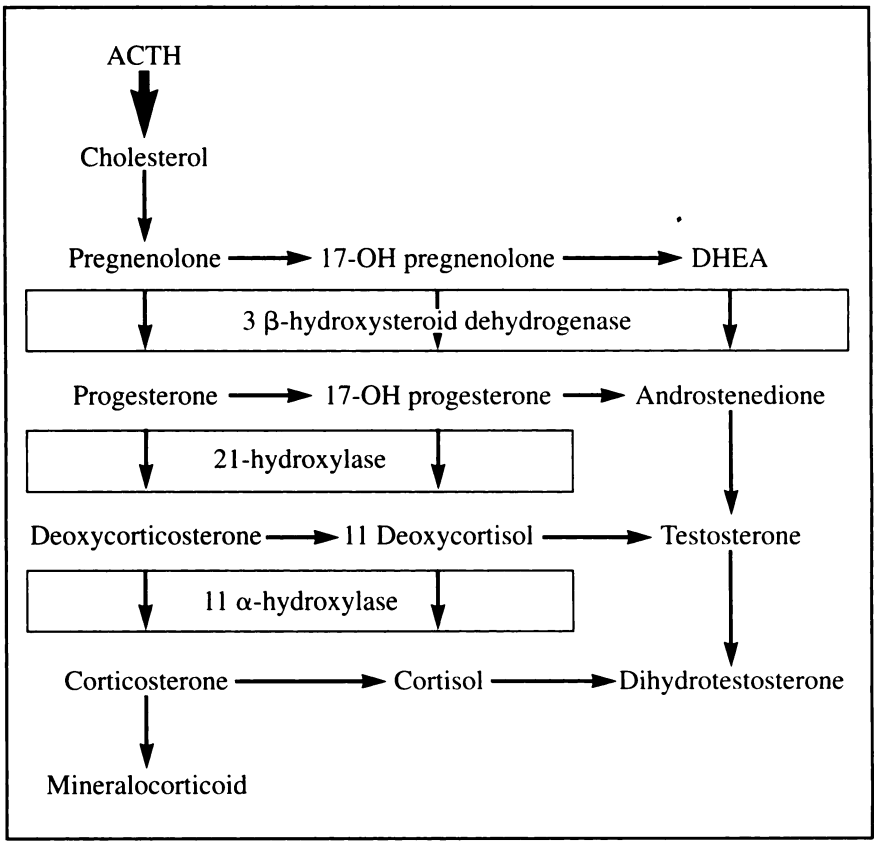

FIGURE 3. Steroid biosynthetic pathway and potential blocks (in boxes) in females.

Serum electrolytes are monitored routinely, primarily to detect hyperkalemia, because salt loss is unlikely in the first week of life. We do not routinely obtain any other laboratory studies in known 46,XX infants or infants whose gonads are not palpable. We believe that rapid karyotyping obviates the need for ultrasonography, which is prone to false-negative results in identifying the presence of a uterus. Nevertheless, some practitioners may wish to obtain ultrasonographic or magnetic resonance imaging (MRI) scans to confirm female pseudohermaphroditism tentatively in advance of the karyotype and 17-OHP results. Although some urologists may obtain ultrasonography or urogenitography in anticipation of repair, these studies generally are not necessary for medical diagnosis.

TABLE 3. Male Psuedohermaphroditism

Dysmorphic syndromes
Defects in testosterone biosynthesis
Cholesterol desmolase deficiency (20,22-desmolase)
17 α-hydroxylase deficiency
3 β-hydroxysteroid dehydrogenase deficiency
17,20 lyase (desmolase) deficiency
17 β-hydroxysteroid oxidoreductase (ketoreductase) deficiency
Leydig cell hypoplasia or hCG resistance
Defects in androgen target tissues
5 α-reductase deficiency
Androgen insensitivity (testicular feminization)
Incomplete resistance
Persistent müllerian duct syndrome
Gonadal dysgenesis
Vanishing testes

TREATMENT

Once 21-hydroxylase deficiency is diagnosed on the basis of elevated levels of serum 17-hydroxyprogesterone, we begin therapy with oral hydrocortisone at approximately 20 mg/m^2 per day divided TID, which can be reduced to 12 to 15 mg/m^2 per day within 1 to 2 weeks. In sick infants or in those presenting with salt loss at a few weeks of age, stress doses of hydrocortisone (50 to 100 mg/m^2 per day) are indicated. In addition to fluids and stress levels of hydrocortisone for initial salt loss and hypotension, oral fludrocortisone 0.1 mg BID is administered initially and then reduced to 0.05 mg BID after a few weeks, if tolerated. The adequacy of replacement glucocorticoid is monitored initially by serum 17-OHP levels and later also by growth parameters and bone age determination. Adequacy of mineralocorticoid dosing is monitored by plasma renin activity and blood pressure. Virtually all female pseudohermaphrodites can be raised as females and will be fertile. In our institution, clitoral recession, opening of the posterior fusion, vaginoplasty, and repair of urogenital sinus are performed within the first 6 months of life.

Male Pseudohermaphroditism (Table 3)

DIAGNOSIS

Incomplete masculinization in the presence of testes generally is due to a failure of the adrenals to synthesize steroid precursors, failure of the testes to produce adequate amounts of testosterone in critical fetal developmental stages, or a lack of androgen responsiveness at the level of target tissues. The male pseudohermaphrodite is more difficult to diagnose and to manage than the female pseudohermaphrodite. Table 3 outlines the many diagnostic possibilities in the 46,XY infant whose genitalia are ambiguous.

External genitalia range from female appearance with a blind vaginal pouch (lower two thirds) to hypospadias and minimal ambiguity. None of the defects in steroidogenesis is associated with remnant müllerian structures because testes will secrete normal amounts of AMH. One or both testes may be palpable in the scrotum or inguinal region, but intra-abdominal testes will complicate the initial diagnosis. If gonads are palpated, an hCG stimulation test to evaluate Leydig cell capacity for testosterone biosynthesis and 5 α-reductase activity should be performed. hCG is given as 1000 U IM daily for 3 days or more, and serum testosterone and dihydrotestosterone levels are measured 24 hours after the final dose. The hCG stimulation test should be used in the initial evaluation of any male pseudohermaphrodite, but it also is valuable to determine whether functioning testes are present when they are small or cannot be located. We regard an hCG-stimulated serum testosterone level greater than 100 ng/dL as evidence of adequate testosterone biosynthesis. Serum should be frozen for subsequent assay for testosterone precursors if hCG-stimulated testosterone levels are low.

Precursors will differentiate deficiencies of cholesterol desmolase, 17 α-hydroxylase, 17,20-lyase, 3 β-hydroxysteroid dehydrogenase, 5 α-reductase, and 17 β-hydroxysteroid oxireductase, all of which appear to be autosomal recessive disorders. We recommend obtaining basal serum levels of pregnenolone, progesterone, 17-OH pregnenolone, 17-OHP, dehydroepiandrosterone (DHEA), androstenedione, testosterone, DHT, and cortisol in the initial evaluation of male pseudohermaphroditism (Fig. 4). Steroid profiles characteristic of each of these defects are available elsewhere.

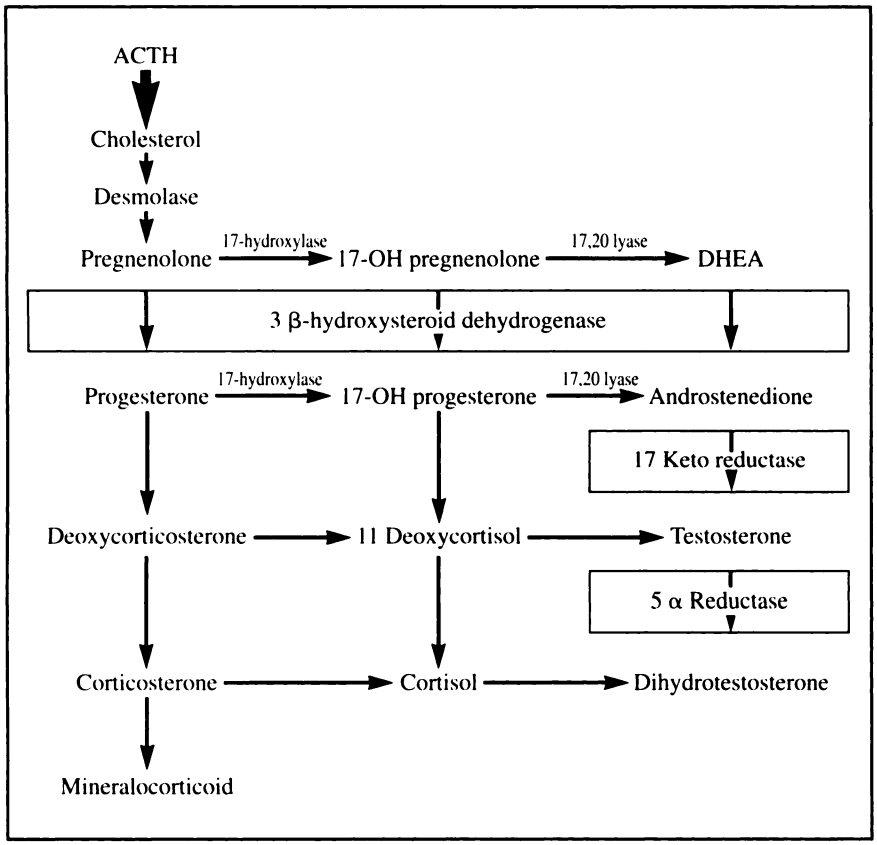

FIGURE 4. Steroid biosynthetic pathway and potential blocks (in boxes) in males.

TREATMENT

Clinically, cholesterol desmolase and 3 β-hydroxysteroid dehydrogenase deficiency are associated with mineralocorticoid deficiency that requires treatment with fludrocortisone, while 17 α-hydroxylase deficiency results in hypertension and laboratory evidence of mineralocorticoid excess. All three defects are associated with elevated serum ACTH levels due to defective cortisol production, are treated with glucocorticoids, and are monitored by serum ACTH levels and plasma renin activity.

5 α-reductase deficiency, in which testosterone is converted inadequately to its more potent metabolite DHT, is characterized by normal internal structures, but ambiguity with chordee, microphallus, bifid scrotum, hypospadias, urogenital sinus, or cryptorchidism is present. The normal mean ratio of testosterone to dihydrotestosterone in infants is approximately 5. In 5 α-reductase deficiency, this ratio is higher. Clinically, some virilization occurs at puberty, with phallic enlargement and development of pubic hair, presumably due to high levels of testosterone.

Partial androgen resistance leads to varying degrees of ambiguity. In contrast, complete androgen resistance (testicular feminization) will not be detected in infancy (unless gonadal tissue can be palpated in the inguinal canal or labia). This diagnosis should be considered at puberty in the context of normal breast development, primary amenorrhea, and sparse pubic hair. Androgen resistance should be suspected in a genetic male neonate who has no obvious diagnosis of a biosynthetic defect, and a trial of testosterone should be implemented by using 25 to 50 mg IM every 3 weeks for a total of three doses. We perform a testosterone trial even before results of the hCG-stimulated testosterone levels are known. If growth of at least 1.5 cm in stretched phallic length cannot be demonstrated after testosterone, depending on the gestational age of the infant, the decision to raise a genetic male as a female must be discussed seriously with the pediatrician, the pediatric endocrinologist, urologist or surgeon, and the family. Androgen resistance can be confirmed by biopsy of genital skin tissue or molecular biology techniques beyond the scope of this review.

Pediatric endocrinologists use both length and diameter of the phallus to assess the potential for sexual function, and failure to achieve adequate phallic diameter with this brief testosterone therapy may lead to the decision to reconstruct the genetic male as a female. Because fertility would not then be a consideration, early prophylactic gonadectomy is recommended.

When etiologic definition of ambiguous genitalia in a 46,XY infant cannot be reached following ascertainment of hCG-stimulated testosterone precursors, testosterone, and DHT levels, remaining diagnostic possibilities include true hermaphroditism and XY gonadal dysgenesis. Because of the variably low or absent production of AMH in these conditions, remnant, normal, or unilateral müllerian structures may be seen on imaging studies such as ultrasonography, MRI, or urogenitography. In our experience, ultrasonography is helpful and easy to obtain but is not as sensitive as MRI for detecting müllerian structures. Ultrasonography also exhibits little reliability in detecting inguinal or intra-abdominal gonads. If XY gonadal dysgenesis or true hermaphroditism (XX or XY) is strongly suspected on the basis of physical, biochemical, and radiologic findings, MRI and subsequent surgical exploration and biopsy are recommended. If the diagnosis is reached from biopsy results, most infants are raised as girls, with gonadectomy being performed by adolescence.

Vanishing testes should be considered in the clinical setting of a chromosomal male who has ambiguous genitalia, unpalpable or small gonads, low hCG-stimulated testosterone levels, and a normal evaluation of steroid precursors. This condition can be responsible for apparent arrest of full male differentiation (ie, microphallus with normal scrotum). For a summary of evaluation, see Figure 5.

Assigning Sex

Problems with assigning sex begin in the delivery room. Obstetricians, nurses, and pediatricians must approach this issue carefully.

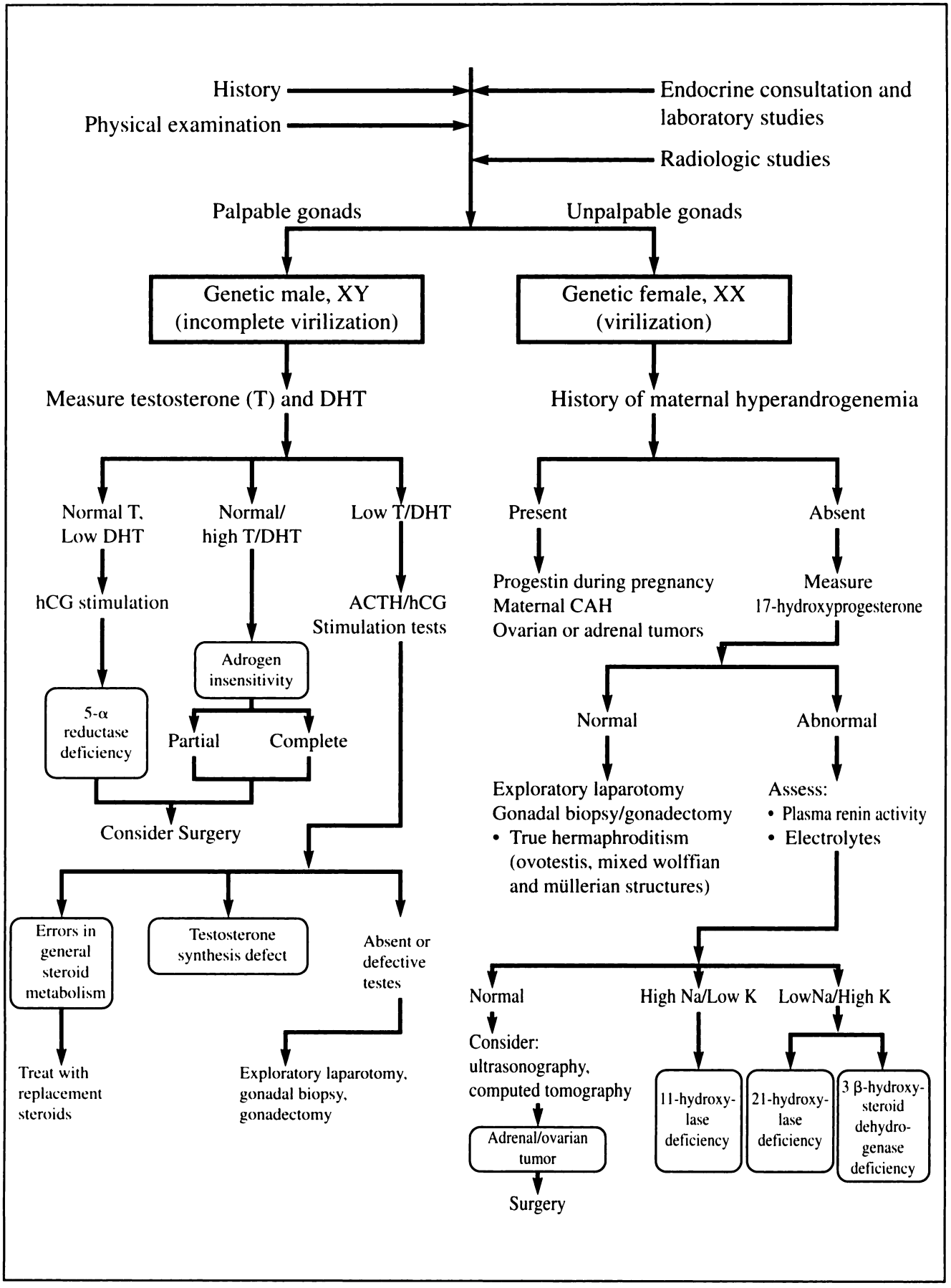

FIGURE 5. Algorithm for evaluating infants who have ambiguous genitalia.

Announcing the probable sex and assigning pink or blue identification cards should be avoided. Discussions with the families should explain that a decision about sex of rearing should wait until test results are known. Critical to the decision of sex assignment is appreciating the potential and capacity for the child's genitalia to function sexually in adulthood. If severe androgen resistance is diagnosed in a chromosomal male, the child should be raised as a female because testosterone replacement would not allow penile growth sufficient for copulation, although the scrotum could be reconstructed surgically. On the other hand, a 46,XX patient who has severe virilization from excess androgens due to CAH would be well-suited to function as a female once medical therapy and surgical reconstruction take place, even though she may appear more like a male at birth. Fertility will be normal, and she will be able to function sexually as a female. Thus, only males are reassigned as females for sex of rearing.

Summary

The newborn whose genitalia are ambiguous presents a challenge to the pediatrician and the family. A clear understanding of the basis of sex differentiation and timely consultation with a pediatric endocrinologist is critical in the evaluation and determination of sex of rearing in a newborn who has ambiguous genitalia. Sex karyotype and a 17-OHP level may suffice in the initial evaluation of female pseudohermaphroditism because most patients will have virilizing CAH. If male pseudohermaphroditism is suspected on the basis of palpable gonads, we routinely obtain a karyotype, basal adrenal steroid levels, and levels of hCG-stimulated serum testosterone and DHT, then consider a testosterone treatment trial. Physicians who care for children who have ambiguous genitalia must appreciate the family's cultural, religious, and psychological needs and avoid determining sex of rearing before accurate diagnosis is reached.

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PIR QUIZ

15. Androgen excess during pregnancy can cause each of the following physical findings on examination of the newborn infant *except*:
    A. Clitoromegaly in the female.
    B. Enlarged penis in the male.
    C. Fusion of the labioscrotal folds in the female.
    D. Normal-appearing scrotum in the male.
    E. Single urogenital sinus in the female.

16. During your examination of a newborn infant, you note ambiguous genitalia but are able to palpate gonads. You suspect that the patient has male pseudohermaphroditism. The diagnostic study of *least* value in establishing a definitive diagnosis is:
    A. Basal adrenal steroid levels.
    B. hCG-stimulated serum dihydrotestosterone level.
    C. hCG-stimulated serum testosterone level.
    D. Karyotype.
    E. Serum electrolytes.

17. You are unable to palpate gonads during your examination of a newborn infant and suspect congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. You order a karyotype. In addition, which of the following studies would you request as the *most* definitive in establishing this diagnosis?
    A. Serum electrolytes.
    B. Serum 11-desoxycortisone level.
    C. Serum 17-hydroxyprogesterone level.
    D. Ultrasonography of the abdomen.
    E. Urogenitography.

18. The most common cause of presentation of ambiguous genitalia at birth is:
    A. Genetic females who have virilizing congenital adrenal hyperplasia due to 21-hydroxylase deficiency.
    B. Genetic males who have androgen resistance in the target tissues.
    C. Genetic males who have testicular synthetic defects in androgen biosynthesis.
    D. Those whose gonadal dysgenesis is incomplete.
    E. True hermaphroditism.