Mini-Review

Ambiguous Genitalia in the Newborn: An Overview and Teaching Tool

Carla Murphy BSc [1], L. Allen MD [2], Mary Anne Jamieson MD [1]

[1] *Department of Obstetrics and Gynaecology, Queen's University, Kingston, Ontario, Canada*
[2] *Hospital for Sick Children, Toronto, Ontario, Canada*

A B S T R A C T

Ambiguous genitalia is a significant example of a disorder of sexual development, in which the external genitalia do not have the typical appearance of either sex. Although the birth of a child with ambiguous genitalia is rare, the emergent nature of the issue demands that healthcare providers have at least a familiarity with the underlying etiologies, the issues, and the initial approach to diagnosis and management. With numerous etiologies, potential difficulties with reaching a diagnosis, and many challenges with immediate and long-term care, the topic of ambiguous genitalia can be daunting. We provide a review of basic embryology, as well as a classification system for understanding the various etiological causes of ambiguous genitalia. The important clinical aspects of diagnosis and management are also highlighted, and a teaching tool has been included to help the reader (or their learners) to solidify information presented. Our overall goal is to provide practical information on ambiguous genitalia and allow the clinician to apply this information to clinically relevant scenarios.
Key Words: Sex differentiation disorders, Ambiguous genitalia, Congenital adrenal hyperplasia, Gonadal dysgenesis, DSD

Introduction

In 2006, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) organized working groups to answer specific questions concerning the management of patients with disorders of sex development (DSD).[1] The consensus statement that resulted was an answer to the call of patients and their support groups who were voicing discontentment with current standards of care and long-term quality of life. Ambiguous genitalia is a significant example of a DSD with numerous etiologies, potential difficulties with reaching a diagnosis, and many challenges with immediate and long-term care. For every thousand live births, 1–2 individuals will be affected by ambiguous genitalia.[2] The emergent nature of answering a parent's anticipatory question of "Is it a boy, or a girl?" underlines the importance of understanding this rather complicated embryological process and developing a sensitive approach to diagnosis and management. Although long-term outcome studies concerning ambiguous genitalia are small in number, some have shown alarming unhappiness with quality of life,[3] and/or a disagreement with their initial gender assignment.[4] We will provide a review of basic embryology, as well as a classification system for understanding the various etiological causes of ambiguous genitalia (Fig. 1). The important clinical aspects of diagnosis and management are highlighted, and then, to help the reader (or their learners) solidify their knowledge, a teaching tool has been included.

Typical Sexual Differentiation

The process of sexual differentiation follows a complicated pathway that requires knowledge of embryology and early endocrinology. Sexual differentiation can be subdivided into four main steps: genetic, gonadal, ductal, and genital differentiation.[5] Embryonic and fetal ages are relative to the time of conception and should not be confused with gestational weeks.

Genetic

Chromosomal sex is typically XX for a female or XY for a male. Genetic sex determination occurs at the time of

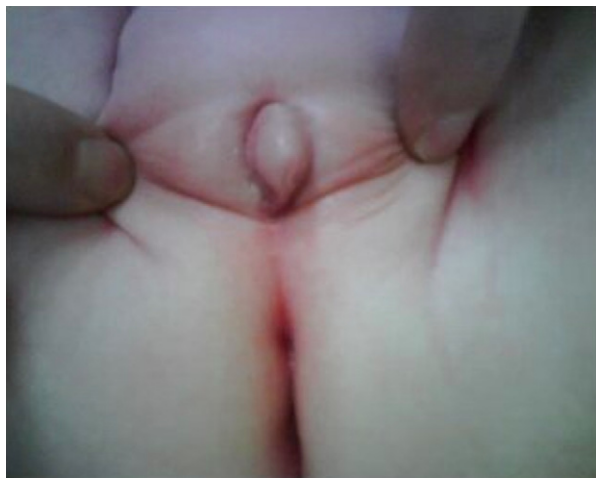

Fig. 1. Photo of infant with ambiguous genitalia.

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Address correspondence to Mary Anne Jamieson, MD, Queen's University, Department of Obstetrics and Gynecology, 99 University Avenue, Kingston, Ontario, Canada K7L 3N6
E-mail address: maj3@queensu.ca (M.A. Jamieson).

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fertilization. Initially, the embryo has all structures necessary to become either sex, and, therefore, can be thought of as 'morphologically bisexual.' At the seventh or eighth week post-conception, the genetic sex then codes for gonadal sex expressed as either primitive ovaries or testes.[6]

Gonadal Sex

At approximately the fifth week following fertilization, the urogenital ridge (ridge in the embryo lateral to the mesentery) thickens, which creates the gonadal ridge. The gonadal ridge remains undifferentiated for two weeks, at which point the first signs of either an ovary or a testis appear (week 7/8).[6]

In a male, the Y chromosome contains the sex-determining region Y (SRY) gene. The SRY gene is, in turn, responsible for the activation of the testis-determining factor (TDF). Early differentiation of the testis is demonstrated by the organization of immature germs cells and somatic cells into testicular cords. Certain somatic cells in the testicular cords mature into Sertoli cells in response to TDF. The Sertoli cells are responsible for secreting the Müllerian-Inhibiting Substance (MIS). MIS plays an important role in ductal differentiation. Soon after the formation of the testicular cords, stromal mesenchymal cells differentiate into Leydig cells, which begin producing testosterone at week 10.[5]

In females, the absence of the SRY gene ultimately results in the formation of an ovary. Without the SRY gene, TDF is not activated and MIS and testosterone are not produced. By the ninth or tenth week the formation of an ovary can be recognized by the absence of testicular features and the meiotic activity of the germ cells (formation of oogonia).[5] Maintenance of the oocyte is achieved through the presence of two X chromosomes—a single X chromosome is sufficient to allow for female sex differentiation, while two X chromosomes are required to maintain the ovaries. This idea is clearly demonstrated in 45,X patients, whose oocytes initially develop, but ultimately undergo atresia.[7]

Ductal Differentiation

There are two paired sets of duct systems involved in genital differentiation: the Wolffian ducts and the Müllerian ducts. Both duct systems are present early on in differentiation. The duct system that predominates in the embryo is determined by the gonadal sex and is later maintained by the production of hormones. In males, the production of MIS causes the degeneration of the Müllerian duct system in an ipsilateral manner. The Wolffian duct is believed to be maintained exclusively by the production of testosterone.[8] By the seventh week, the Wolffian system develops into the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts.[6]

In females, the absence of MIS allows for the preservation of the Müllerian duct system, while the Wolffian duct remains undeveloped in the absence of testosterone. The Müllerian duct matures into the fallopian tubes, uterus, and the upper vagina by the eighth week[6] (Fig. 2 A&B[7]).

External Genitalia

The differentiation of the external genitalia begins at week eight (Fig. 3),[9] which results in recognizably female or male genitalia by three months. Initially, female and male embryological development is the same. In the beginning, the fetus has a cloacal membrane that is bordered laterally by a pair of cloacal folds and genital swellings. When the cloacal folds fuse ventrally they create the genital tubercle. By the seventh week, the cloacal membrane has developed into the urogenital membrane anteriorly and the anal membrane posteriorly (each of which eventually rupture to form corresponding orifices). The cloacal folds eventually develop into the urogenital folds.[6] From this point, the differentiation into male or female genitalia is a direct consequence of the presence or absence of androgens, and the sensitivity of the developing genitalia to these androgens.

In males, androgen stimulation during weeks nine through twelve results in masculinization of the external genitalia. The genital tubercle elongates to form the phallus, while the urogenital folds elongate and fuse, resulting in the formation of the penile urethra. The corpus spongiosum is a result of the differentiation of the mesenchymal masses around the penile urethra. At the end of the third month, a fold of skin from the base of the glans penis will have grown distally and created the prepuce. The scrotum is the end result of genital swelling with fusion and rugation.[6] The descent of the testis from its origin at the urogenital ridge into the scrotum can be divided into two phases: transabdominal and inguinoscrotal. The transabdominal phase requires the presence of androgens to induce the regression of the cranio-suspensory ligament, which releases the testis for descent. Insulin-like 3 (produced by Leydig cells) has been shown in mouse models (and theorized to play the same role in humans) to help anchor the testis in the inguinal region, while MIS has also been hypothesized to play a role in this phase of descent. Androgens play a prominent role during the inguinoscrotal phase with the end result of fully descended testes.[10]

Feminization of the external genitalia (which in fact reflects a lack of masculinization), begins during week eight due to the absence of androgen production (or its bioavailability). The genital tubercle matures into the clitoris, and the labia majora develop from the genital swellings. The caudal urogenital sinus shortens and widens to become the vaginal vestibule and the urogenital folds develop into the labia minora.[6]

The process of sexual differentiation is a complex web of genes, hormones, and receptor sensitivity that usually results in typical male or female genitalia. However, in rare cases, the progression from "morphologically bisexual"[6] to distinctly "male" or "female" is disrupted, which can result in disorders of sexual development (DSD) including ambiguous genitalia.

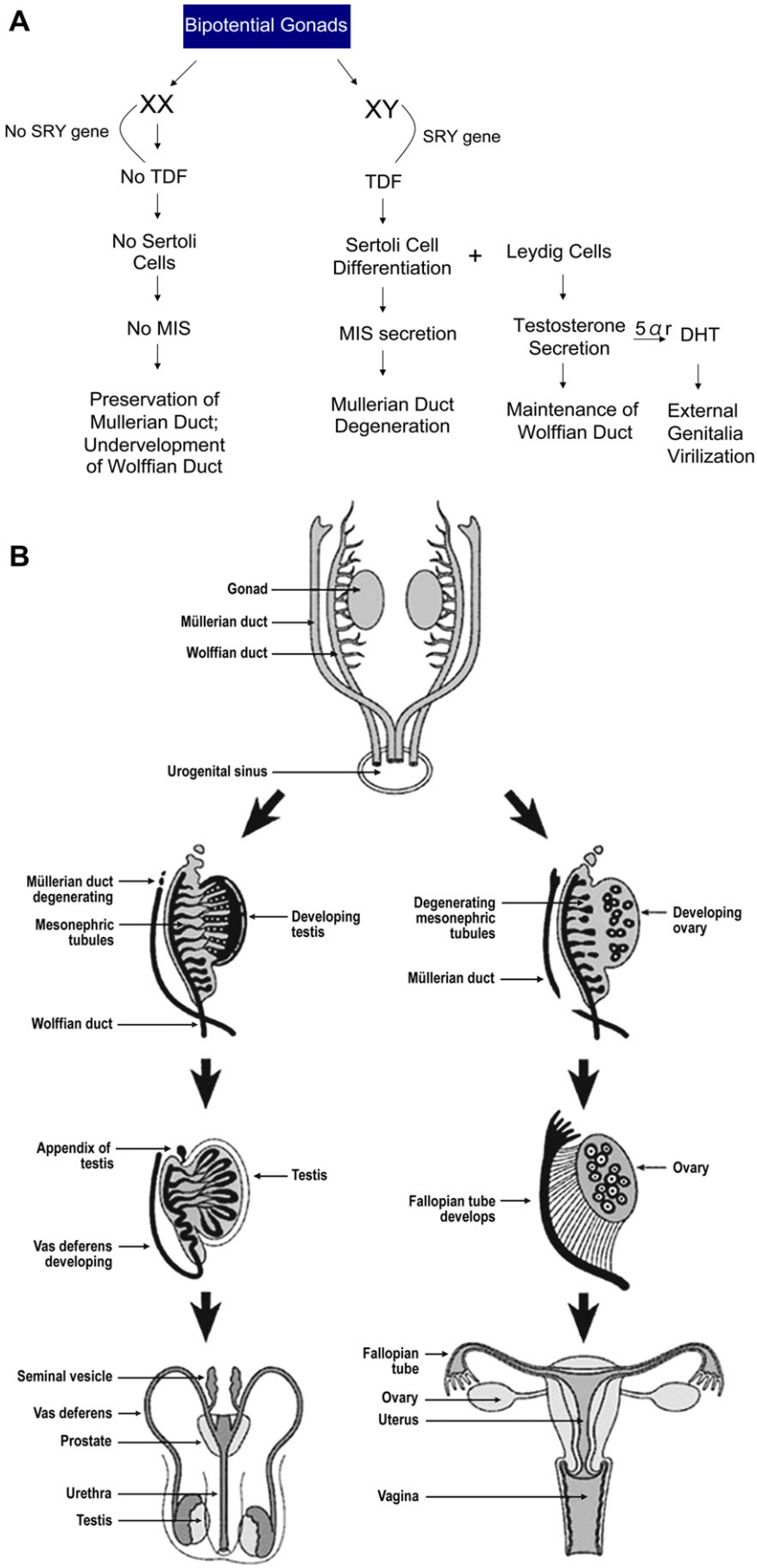

Fig. 2. A, Ductal differentiation. SRY, sex-determining region Y; TDF, testis determining factor; MIS, Müllerian inhibiting substance; DHT, dihydrotestosterone (potent androgen); 5αr, 5 alpha reductase (authors' original figure); B, Ductal differentiation schematic. (Fig 2B Reprinted with permission from Ambiguous genitalia in the newborn. Pediatric and Adolescent Gynecology 2005, p. 59.)

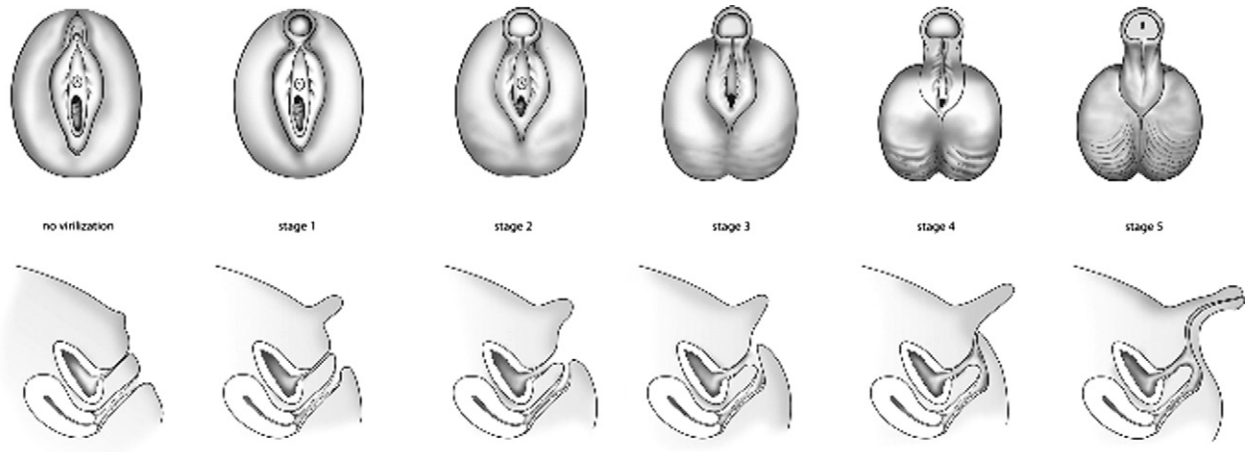

Fig. 3. Prader Staging and virilization of external genitalia. (Reprinted with permission from Allen, L: Disorders of sexual development. Obstetrics and Gynecology Clinics of North America 2009; 36(1): 25-45.)

Atypical Sexual Differentiation

The coordinated set of steps involved in sexual differentiation rarely becomes disordered, but if a disturbance occurs, ambiguous genitalia can result. In order to sort through the various genotypes, phenotypes, and etiologies of ambiguous genitalia, the following classifications will be used: 46,XX DSD, 46,XY DSD (which will include malformation syndromes), and gonadal disorders (ovotesticular DSD and gonadal dysgenesis).[7]

46,XX DSD

Individuals with 46,XX DSD will typically have female internal genitalia (Müllerian-derived structures and ovaries). However, the external genitalia will become over-virilized as a result of *in utero* androgen exposure.[11] The two major etiologic classes of 46,XX DSD are exposure to fetal androgens and exposure to maternal androgens. The main source of fetal androgens is from a condition known as congenital adrenal hyperplasia (CAH). Maternal androgen conditions are usually a consequence of adrenal or ovarian tumors,[12] although the administration of exogenous androgenic medications is also a potential and preventable cause of ambiguous genitalia.[13]

CAH (over-virilizing)

CAH does not always result in ambiguous genitalia, but it is the most common cause of genital ambiguity in 46,XX patients. CAH is a term used to represent a group of autosomal recessive disorders that result in impaired steroidogenesis, which can be subdivided into virilizing, and non-virilizing forms.[14] In the case of virilizing CAH, the production of cortisol is blocked, which allows for proximal steroid precursors to build up, and the negative feedback of cortisol on the hypothalamus-pituitary-adrenal axis is lost. Without this negative feedback, the amount of adrenocorticotropic hormone (ACTH) secreted by the pituitary increases and eventually leads to increased adrenal androgen synthesis and adrenal cortical hyperplasia.[14] There are several steps involved in the conversion of cholesterol to cortisol, aldosterone, and testosterone. With each step there is a potential for enzyme mutation and dysfunction. Fig. 4 depicts the essential steps in the steroidogenesis pathway and the enzymes responsible for each modification. The outcome of the enzyme mutation depends mainly on the degree of dysfunction of the enzyme. Therefore, the degree of genital ambiguity will range from mild labioscrotal fusion ± clitoromegaly to severe labioscrotal fusion and a phallus similar to an unaffected male.[7] Currently, several mutations in the steroidogenic pathways are known to cause genital ambiguity, although some are much more common than others, and while most will over-virilize a female (46,XX DSD), others will prevent a male fetus from virilizing fully (see 46,XY DSD).

The most common enzyme defect that causes CAH and that results in over-virilization of the 46,XX newborn is a mutation in the gene coding for the enzyme 21-hydroxylase (Fig. 4 ----). This enzyme is responsible for the conversion of 17-hydroxyprogesterone (17OH-progesterone) to 11-deoxycortisol in the cortisol synthesis pathway. 21-hydroxylase deficiency exists in two forms: the classical form, which includes salt-wasting and simple virilizing 21-hydroxylase deficiencies, and the milder, nonclassical form.[14] The salt-wasting that occurs in some cases of 21-hydroxylase deficiency is a result of the enzyme's role in converting progesterone to deoxycorticosterone, which is a precursor to aldosterone. Therefore, when the enzyme is mutated there is a decrease in aldosterone synthesis and an increase in its precursor proteins. Aldosterone is a hormone that causes sodium reabsorption and potassium secretion in the distal tubule of the kidney. If aldosterone cannot be synthesized, one of the body's main sodium reabsorption pathways is blocked, and salt-wasting takes place. Because of the potential for a life-threatening salt-wasting crisis, it is standard for any neonate presenting with ambiguous genitalia and impalpable gonads to be worked up for CAH.[12] In the case of the nonclassic form of 21-hydroxylase deficiency, the genitalia are often normal. If the newborn does not suffer from salt-wasting, this enzyme

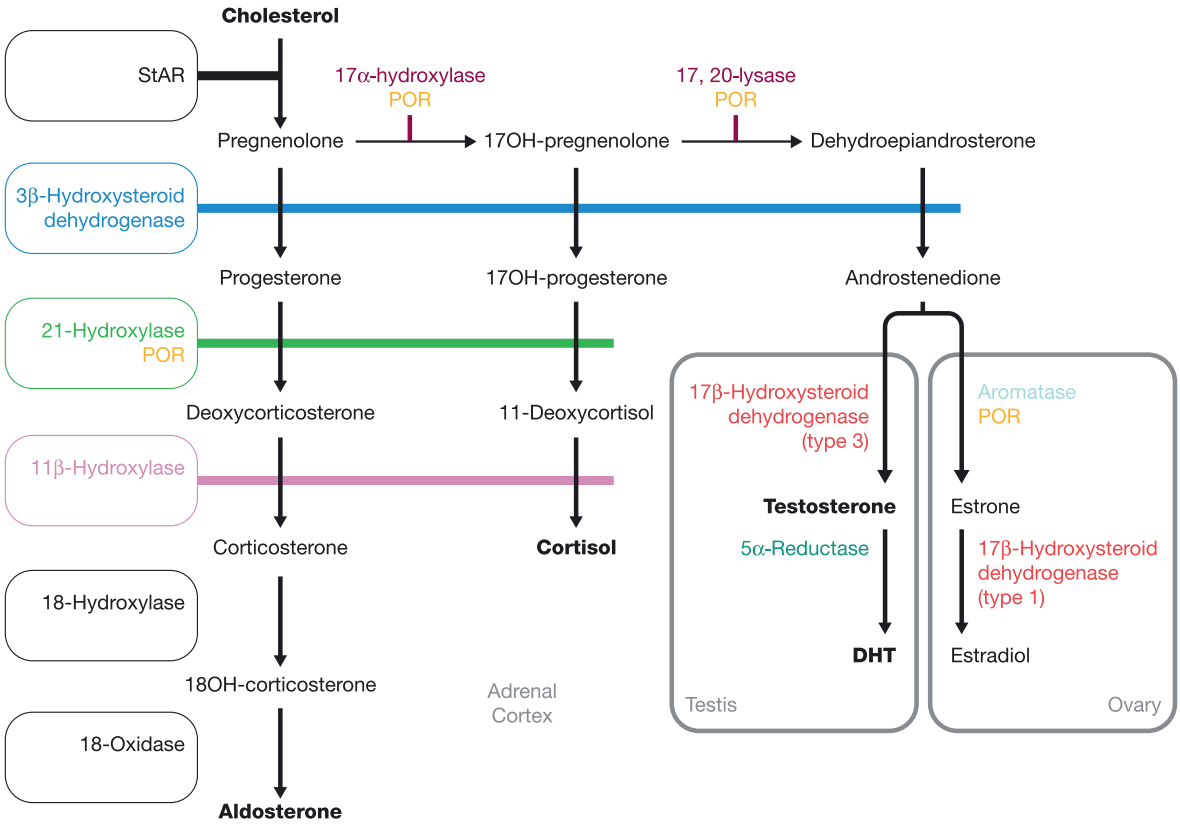

Fig. 4. Diagrammatic representation of steroidogenesis pathway. The colors of the enzymes correspond to colors within the text and with Table 1. POR, P450 oxioreductase. Abbreviations: s = serum; N = normal; Viril = virilizatin; 17OHPro=17-hydroxyprogesterone; 17OHPreg = 17-hyroxypregnenolone; DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone; 11-deoxy = 11-deoxycortisol; Andro = androstenedione; Testo = testosterone; cortico = corticosterone; DHT = dihydrotestosterone; AR = androgen receptor; HTN = hypertension; ACTHS = ACTH stimulation test

deficiency can be missed and the child may present later in life with premature pubarche and/or hyperandrogenism (and possibly virilization) at adrenarche.[14]

46,XX newborns with 21-hydroxylase deficiency have normal internal genitalia. The uterus and the ovaries will be present and in the correct locations. The external genitalia virilize in response to the excess secretion of androgens.[11] The extent to which the external genitalia virilize in these patients is dependent on the severity of the mutation and the degree of enzyme deficiency. Therefore, the range of phenotypes is broad and varying. Conversely, 46,XY neonates that suffer from this enzyme deficiency often have typical sexual differentiation, but may have hyperpigmentation of the external genitalia from excess ACTH stimulation.[14]

There are other less common enzyme deficiencies that can lead to over-virilized 46,XX newborns. These include 3β-hydroxysteroid dehydrogenase deficiency (Fig. 4 ----), 11β-hydroxylase deficiency (Fig. 4 ----), P450-oxioreductase (POR) deficiency (Fig. 4 ----), and placental aromatase deficiency (Fig. 4 ----). The pathways can be reviewed in Fig. 4; however, the details of each of these deficiencies will not be discussed here. Some important points to remember include:

- 46,XY individuals with 3β-hydroxysteroid dehydrogenase deficiency will also show ambiguous genitalia because dehydroepiandrosterone cannot be converted into the androgens necessary for virilization. The virilization seen in 46,XX DSD is due to a small amount of peripheral conversion of DHEA to testosterone by an extragonadal form of the 3β-hydroxysteroid dehydrogenase enzyme.
- Individuals with 11β-hydroxylase deficiency may suffer from glucocorticoid deficiency, excessive adrenal androgen secretions, hypertension, and hypokalemia (deoxycorticosterone is a weak mineralocorticoid).
- Both 46,XX and 46,XY individuals with POR deficiency may present with ambiguous genitalia, although postnatal virilization will not occur and there may be several extragonadal malformations.[14]
- Placental aromatase deficiency results in an accumulation of placental androgens and under-production of placental estrogens, which can over-virilize both the mother and the 46,XX fetus.[14]

Other Etiologies of 46,XX DSD

Exposure to maternal androgens is a rare cause of over-virilization of 46,XX newborns, although it should not be overlooked during the period of diagnosis. The main causes of excess maternal androgens are endogenous secretions from adrenal and ovarian tumors. Polycystic ovary syndrome can rarely cause virilization as well.[11] Exogenous

androgen or progestin ingestion is another rare cause of ambiguous genitalia in the 46,XX child.[7]

46,XY DSD

The three main etiologic groupings that lead to under-virilized genitalia in an XY neonate are abnormal testis determination (which will be discussed under the heading of gonadal dysgenesis), defects in androgen biosynthesis and metabolism, resistance to androgens, and malformation syndromes. It is important to note that a definitive diagnosis/etiology for a newborn with 46,XY genotype is often difficult to establish, and there are many times when nothing conclusive is discovered.

Defects in Androgen Biosynthesis and Metabolism

Neonates with defects in androgen biosynthesis and metabolism typically have normal testes, but the adrenal gland contribution to androgen production is compromised or the conversion of testosterone to dihydrotestosterone (the androgen that specifically acts on the external genitalia) is inhibited. As with over-virilized females, certain CAH enzyme deficiencies in the steroidogenesis pathways can result in ambiguous genitalia of the 46,XY newborn.

CAH (undervirilizing)

The following enzyme deficiencies can result in under-virilization of the 46,XY newborn:

- 3β-hydroxysteroid dehydrogenase deficiency[14] (Fig. 4 ----)
- 17α-hydroxylase/17,20-lysase deficiency is caused by a defect in one gene coding for two enzymes (CYP17)[13] with results that range from female external genitalia to ambiguous genitalia. Hypertension is a common feature of this deficiency. 46,XX neonates with this defect will be unaffected.[11] (Fig. 4 ----)
- 17β-hydroxysteroid dehydrogenase deficiency leads to a 46,XY infant with under-virilized genitalia, a male duct system and inguinal testes.[11] (Fig. 4 ----)
- Steroid acute regulatory protein (StAR) gene mutation results in congenital lipoid adrenal hyperplasia, a build up of cholesterol that can be toxic to the adrenal glands, and under-virilization of the genitalia.[11] (Fig. 4 ----)
- As mentioned previously, POR deficiency (Fig. 4 ----) can lead to ambiguous genitalia of the XY newborn. Again, post-natal virilization will not occur and several extra-gonadal malformations may exist.

5α-reductase Deficiency

Another example of a defect in androgen biosynthesis and metabolism is 5α-reductase deficiency (Fig. 4 ----). 5α-reductase has two isoenzymes, where 5α-reductase 2 is linked to ambiguous genitalia. Typically, this enzyme converts testosterone to dihydrotestosterone (DHT), which, in turn, acts on the genital tubercle and swellings, and the urogenital sinus to promote external genitalia formation and the formation of the prostate. When this enzyme is not properly functioning, there are normal to elevated levels of testosterone, decreased plasma levels of DHT, and an increased testosterone/DHT ratio.[15] The low levels of DHT—an androgen that is more potent than testosterone—results in phenotypic variability, although female genitalia with some degree of masculinization is the most common. This severe form of ambiguous genitalia often presents with a clitoris-like phallus, a bifid and empty scrotum (the testes are often found in the abdomen or inguinal canal), and pseudovaginal perineoscrotal hypospadias. The Wolffian structures, namely the seminal vesicles, vas deferens, and epididymis, are normal.[16] At puberty, there is often an increase in muscle mass, a deepening of the voice, growth of the phallus occurs, pubic hair appears, and the testes will descend into the scrotum. However, mature sperm is often absent. The extreme changes at puberty have been shown often to cause a shift in gender assignment from female (if that is the gender assigned at birth) to male.[16]

Resistance to Androgens

Ambiguous genitalia can result even if the necessary androgens are synthesized correctly. In this situation, the defect often lies in the sensitivity of target tissue to the androgens. Two forms of androgen insensitivity syndrome have been described: complete (CAIS) and partial (PAIS). These are recessive conditions that are connected to the X chromosome.[16] Both testosterone and DHT bind a transcription factor referred to as an androgen receptor (AR), which helps regulate gene expression in target tissue. When there is a defect in the AR, testosterone and DHT cannot properly participate in male sexual differentiation. CAIS is often thought of as a monomorphic syndrome, in which the neonate will have female external genitalia and the appearance of bilateral inguinal hernias (which are the undescended testes). The testicles are able to secrete MIS, which leads to the degeneration of the Müllerian structures and no Müllerian derivatives can form—no fallopian tubes or uterus. There often is a vagina, although it is blind and small in size. At puberty the classic signs are primary amenorrhea, normal breast development (androgens converted to estrogens), but no pubic or axillary hair, and no acne. Neonates with CAIS have been shown to exhibit 'female sexual behavior,' and these children are almost always initially assigned a female gender.[16]

PAIS is a much more heterogeneous syndrome, with extreme variability in the phenotype of the external genitalia. Classifications such as Prader (Fig. 3) or Quigley's can help to qualitatively describe the varying degrees of sexual ambiguity. The range of ambiguity encompasses syndromes that closely resemble CAIS all the way to infertile males without genital ambiguity. The mildest end of the spectrum has classically been referred to as Aiman's syndrome, and more recently minimal AIS.[16]

Malformation Syndromes

Malformation syndromes best fit into the classification of 46,XY DSD and include chromosomal abnormalities, single gene abnormalities, and associations.[7] An example of a chromosomal abnormality that can present with, among other things, ambiguous genitalia is trisomy 13. Some common examples of single gene syndromes are Smith-Lemli-Opitz

syndrome (deficiency of the enzyme 3 beta-hydroxysteroid-delta 7-reductase), and Beckwith-Wiedemann Syndrome (whose etiology is still uncertain). An example of an association is VACTERAL (vertebrae, anus, cardiovascular tree, trachea, esophagus, renal systems, ambiguous genitalia, and limb buds).

Gonadal Disorders

The term gonadal disorders encompasses both ovotesticular DSD (ODSD) and gonadal dysgenesis.

Ovotesticular DSD (ODSD)

In ODSD, the newborn has both ovarian and testicular tissue. There are various combinations of these two types of tissues: one ovary and one testis, 2 ovotestes, or one ovotestis partnered with either an ovary or a testis. The external genitalia can be male or female, but most often it is ambiguous in nature. The most common genotype (over half of patients) is 46,XX, one third of patients are chimeric (46,XY/46,XX) or mosaic (46,XY/47,XXY or 45,X/46,XY), and only a small minority have a 46,XY genotype.[7] 46,XX patients may have translocation of the SRY gene; however, in most cases the genes responsible for ODSD have yet to be identified.[11] The degree of virilization of the external genitalia depends heavily on the ability of the testicular tissue to secrete testosterone, and whether or not the Müllerian ducts have matured into female structures. Often, the differentiation of internal and external genitalia will coincide with the gonad on the ipsilateral side. For example, if a testis is present on the left side, the Wolffian duct on the left side will remain and differentiate into the appropriate structures and the left side of the Müllerian system will regress (ipsilateral Müllerian inhibiting substance).[7]

Gonadal Dysgenesis

In gonadal dysgenesis, the typical gonad is replaced with a dysgenetic testis or a "streak gonad." There are two different categories of gonadal dysgenesis—pure and partial.

In pure (complete) gonadal dysgenesis, the genotype can be either 46,XX, 46,XY, or a Turner syndrome karyotype (45,XO, or 45,XO/46,XX). The neonate with pure gonadal dysgenesis will have streak gonads, look female at birth, and often present later in life with delayed puberty and primary amenorrhea. Sawyer syndrome is a rare form of pure 46,XY gonadal dysgenesis where the external genitalia are female and the uterus and fallopian tubes are present. It is hypothesized that Sawyer syndrome is caused by a mutation in the SRY gene, although in the majority of cases the etiology is unknown.[11]

In partial gonadal dysgenesis, there is partial testicular development. Partial dysgenesis includes mixed gonadal dysgenesis (MGD) and testicular or ovarian regression.[11] In MGD there is a streak gonad (or no gonad) on one side and a testis—often dysgenetic—on the contralateral side. The genotype is often 45,XO/46,XY, although it can be 46,XY. The phenotype will reflect the amount of androgen production that can be supported by the dysgenetic testis.[7] With two dysgenetic testes, patients often have ambiguous genitalia, low levels of testosterone, and there can be persistent Müllerian structures.[17] Finally, in gonadal regression there was thought once to be a testis or ovary present, but at some point it has atrophied and cannot wholly fulfill the duties of external genitalia formation. [18,19]

For any condition with a dysgenetic gonad, the potential for gonadal neoplastic changes is increased and thorough follow-up or removal of the dysgenetic gonad is recommended,[11] as will be discussed under Medical Management.

Diagnostic Work-Up

Although the diagnosis of ambiguous genitalia is rare, the ramifications of an unprepared physician can resound for years to come, with both the parents and the child. Many physicians that care for patients with ambiguous genitalia agree that more work needs to be done in the area of long-term outcome research and in the continuous development and improvement of management strategies. However, protocols have been designed based on the current medical and psychosocial knowledge. Like any condition, the main components of diagnosis and care are history taking, physical exam, and laboratory investigations (Fig. 5). The results of all collected data will help the multidisciplinary team and parents decide what action is immediately necessary and what other interventions can and should wait.

A great resource for physicians and parents is the Accord Alliance website (www.accordalliance.org), which provides practical information on many aspects of DSD and can help facilitate discussions between the healthcare team and the family.

Before getting started on the history, physical, and investigations, it is important to note that the need for a multidisciplinary approach is emphasized in many papers. For example, the Clinical Guidelines for the Management of Disorders of Sex Development in Childhood,[20] published in 2006, states:

> "The multidisciplinary team can play a critical role in creating a climate of commitment to the health and welfare of children born with DSDs, as well as to their families. It can make possible the provision of excellent care that has as its goal the long-term physical and psychological well-being of individuals with DSDs and of their families. … Additionally, the challenges brought on by the environment of a developing child and family will require ongoing assessment and possible changes to established treatment goals."

Within these guidelines (available at the Accord Alliance website), an ideal protocol has been laid out that strives to minimize harm to both the patient and the family. Although the guidelines recognize that no one hospital or team of caregivers may be able to follow the protocol perfectly, the underlying theme of thoughtful and mindful practice, as well as minimizing tests and harm to the patient and their family should be adopted by all multidisciplinary teams.

The Consensus Statement on Management of Intersex Disorders, also published in 2006, aimed to create a resource that would fill in some of the gaps in patient care that had been recognized by experts in the field.[1] The

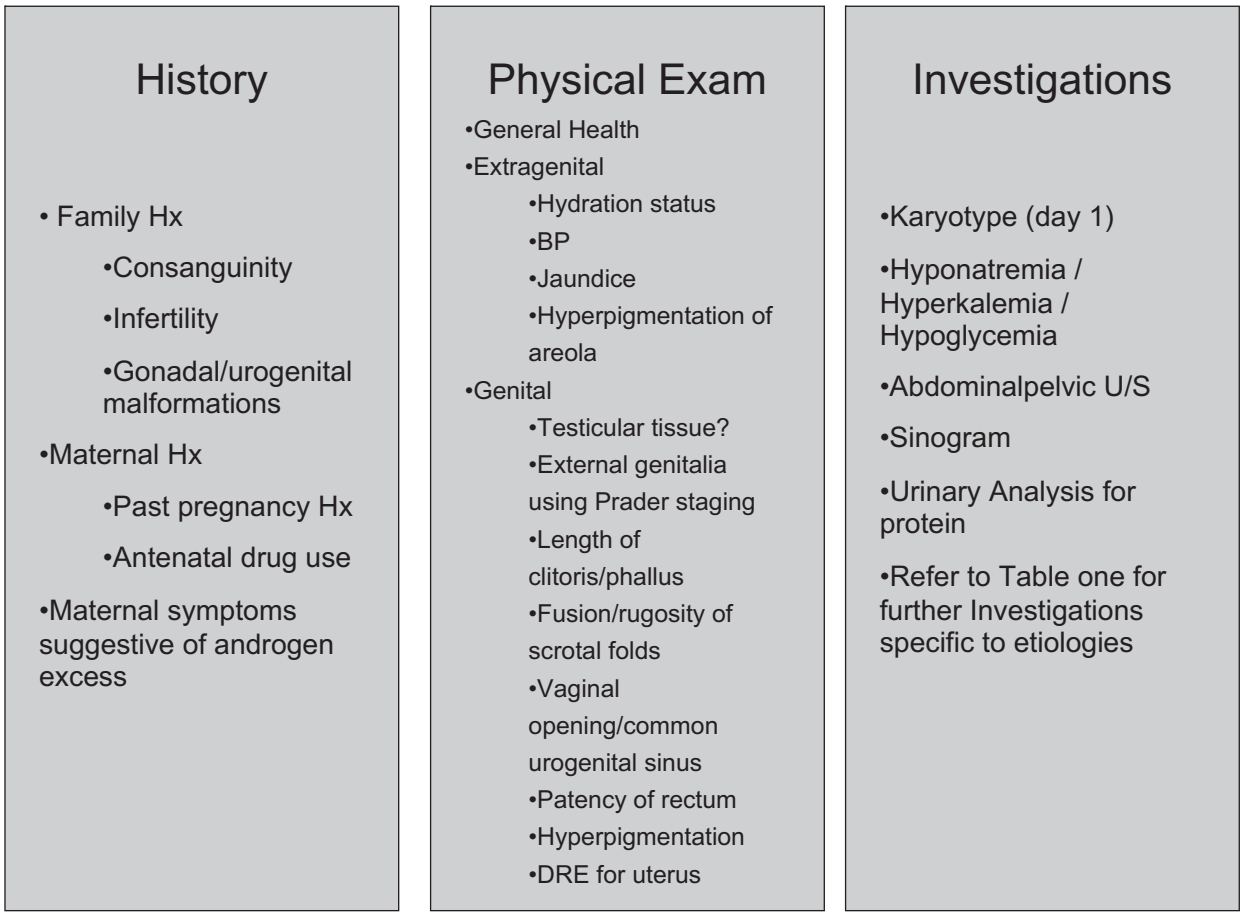

Fig. 5. A summary approach to diagnosis of ambiguous genitalia.

authors describe good first line investigations, and an excellent overall approach to the care of a patient with DSD. There are also several good and current resources for the approach to a child with ambiguous genitalia specifically. The following suggestions for history, physical, and investigations draw strongly on the knowledge and research of Ogilvy-Stuart and Brain,[21] who published Early Assessment of Ambiguous Genitalia in 2004, as well as the work of Shomaker, Bradford, and Key-Solle,[22] who published How to Treat the Newborn with Ambiguous Genitalia in 2009.

History (Fig. 5)

The history needs to identify any positive family history, such as genital or urological anomalies, especially a history of ambiguous genitalia. A history of consanguinity (which would increase the likelihood of an autosomal recessive condition) or infertility would also be significant. A maternal history of spontaneous miscarriages, still-births, neonatal deaths (which could indicate an undiagnosed adrenal crisis), and/or drug use during the pregnancy that may have lead to virilization could contribute to making the diagnosis. Maternal symptoms also need to be taken into account; for example, signs of androgen excess (hirsutism, virilization) which would suggest a possible maternal endocrinopathy. Questions that can be mistaken for placing blame on the parents should be avoided, and circumventing terms such as 'it' and 'abnormal' when referring to the child will help the discussion move in a more positive direction. Using the baby's name or terms such as 'your baby', 'your child', and 'little one' may be more appropriate in this situation.

Physical Exam (Fig. 5)

The parent(s) and the immediate family of the neonate with ambiguous genitalia may be in a serious state of distress; therefore, parents should be reassured that physical exams are performed to optimize the care of the child and not to put them on display. Also, in a learning center, the attending physician may wish to limit the number of learners that are present at each visit.[20] Of course, all components of a routine neonatal exam are important, but here we will focus on those parts of the exam crucial to ambiguous genitalia work-up. There are several genital and extragenital signs to look for, and it is also important to identify any dysmorphic features that could suggest multiple anomaly syndromes or genetic syndromes.

Initially, the general health of the newborn should be noted including hydration status, urine output, weight, and blood pressure—all of which may be altered in infants with CAH. Hyperpigmentation of the areola, hypertension, and

dehydration are signs of excess ACTH or mineralcorticoids and can also be present with CAH.

Next, a careful and thorough search for testicular tissue in the inguinal canal, labioscrotal folds, and the scrotum should be performed—the presence of any testicular tissue excludes in most cases the diagnosis of 21-hydroxylase deficiency. Also the external genitalia can be described using Prader staging, which describes the degree of virilization using stages I (female with clitoromegaly) to V (male with hypospadias). The length of the clitoris or phallus should be noted, along with any sign of chordee. A typical (full term) newborn penis measures 3.5 +/− 0.4 cm with measurements less than 2.3–3.6 being consistent with micropenis. The clitoral size of a newborn is typically 2.0–8.5 mm in length and 2.0–6.0 mm in width.[9] The degree of fusion and the rugosity of the scrotal folds, and the presence or absence of a vaginal opening or common urogenital sinus should be recorded. Patency of the rectum and any hyperpigmentation of the genital skin are important observations. The presence of a uterus may be appreciated on digital rectal examination.

Lab Investigations (Fig. 5)

It is important to remember that the goal of the initial investigations is to determine the classification of the child (e.g., 46,XY DSD) and avoid a life-threatening salt crisis (which does not occur until the 4^{th}–15^{th} day of life). The following should be carried out in all neonates with suspected ambiguous genitalia—a blood sample should be sent for urgent karyotyping, LH, FSH, and androgen levels (including testosterone, DHEA, androstenedione, DHT, and 17-OHPro). Electrolytes and glucose should be closely monitored, and imaging including an abdopelvic ultrasound should be done. Imaging is useful in identifying internal anatomy, confirming the presence of a uterus, identifying most gonads, and outlining the renal and urinary system. Occasionally a sinogram may be necessary to determine the anatomy of the lower genital tract and the lower urinary system when there seems to be a common urogenital sinus. Abnormalities on urinalysis may be secondary to a concurrent renal anomaly.

46,XX DSD

In any 46,XX patient with impalpable gonads, the finding of increased serum levels of 17OH-progesterone is enough to make the diagnosis of 21-hydroxylase deficiency. The level of 17OH-progesterone can be high within the first 48 hours of life in normal babies and unwell or preterm babies that do not suffer from CAH. Another test that can help identify 21-hydroxylase deficiency and/or adrenal insufficiency is the ACTH stimulation test, which looks at the adrenal response to synthetic ACTH (by monitoring the cortisol response as well as looking at precursor:product ratios post administration of synthetic ACTH). Other tests that can confirm CAH (of various enzyme deficiencies) are levels of androstenedione and testosterone, as well as the plasma renin activity. Serum levels of potassium and sodium should be monitored when the diagnosis of CAH is made. To review the various CAH-related enzyme deficiencies, their under-produced adrenal products, their over-produced precursors, and their clinical stigmata, see Table 1 and Fig. 4.

46,XY DSD

For 46,XY DSD infants, an important test for many etiologies is the hCG test. hCG is similar to LH (luteinizing hormone) and can demonstrate many enzyme and receptor abnormalities. Essentially, baseline testosterone, DHEA, androstenedione, and DHT are taken, and then peak values are measured after hCG has been injected. Some clinicians will defer this test until after 2 weeks of life due to an increase in activity of the infant's gonads. See Table 1 for specific outcomes in various deficiencies. MIS is another useful marker in 46,XY DSD. MIS is a reliable marker for testicular tissue function and can be helpful in AIS and ODSD (high in the former and low in the latter). An ACTH stimulation test can be useful in confirming enzyme deficiencies as mentioned above.

As mentioned above, 46,XY infants that suffer from CAH may have 17α-hydroxylase/17,20 lyase, 3β-hydroxysteroid dehydrogenase or 17-β-hydroxysteroid dehydrogenase or StAR enzyme deficiencies. For each of these cases, the baseline and post-hCG testosterone levels will be low and there will be high levels of testosterone precursors. As with overvirilizing CAH, an ACTH stimulation test will demonstrate adrenal insufficiency in undervirilizing CAH. Refer to Table 1 for more specific serum levels.

Shomaker et al address 46,XY infants without an adrenal insufficiency by classifying them into those that will virilize further and those that will not. Giving three doses of hCG 24 hours apart and measuring the DHEA, androstenedione, testosterone, and DHT levels can help predict virilization potential. Bearing in mind that patients who will virilize further at puberty will often have a male gender identity, further diagnosis, and gender assignment in this category is difficult and can take some time. In the case of PAIS, genital skin biopsies may be needed to test androgen receptor activity (on genital skin fibroblasts), or a mutation in the AR gene can be sought through DNA analysis. Refer to Table 1 for further details.[22]

Gonadal Disorders

Infants with gonadal differentiation or chromosomal disorders are not at risk of adrenal insufficiency. Their initial gender assignment will be based on many factors and will require input from all members of the multidisciplinary team and the parents. In patients with gonadal dysgenesis, an hCG test and a gonadal biopsy may determine the functioning state of the gonadal tissue. Consideration of testicular functioning at puberty, potential phallic development, and gonadal location will also help guide gender assignment.

Medical and Surgical Treatment

Firstly, patients with salt-wasting CAH disorders need to be treated to avoid a crisis. This treatment includes glucocorticoid replacement with hydrocortisone and

Table 1
Summary of Underlying Conditions Causing Androgen Excess or Deficiency

Enzyme Deficiency	Product Deficiency	Precursor Excess (HCG stim test)	Product Excess	Clinical	Investigations	Colour code
21α	Cortisol, Aldosterone	Progesterone 17-OHP	Adrenal Androgens	Over-viril 46XX, low Na, High K	↑ (s) 17OHPro ACTHS↓/absent cortisol response	
3β	Cortisol, Aldosterone, Testosterone	Pregnenelone, 17OHPreg, DHEA	DHEA	Over-viril 46XX or Under−viril 46XY, Low Na, High K	↑(s) 17OHPreg, DHEA ACTHS↓/absent cortisol response	
11β	Aldosterone Cortisol	Deoxycorticosterone 11-deoxycortisol	Adrenal Androgens	Over-viril 46,XX Low K HTN	↑ (s) 11-deoxy ACTHS↓/absent cortisol response	
P450 (POR)	Variable	Variable	Variable	Over-viril 46,XX or Under-viril 46,XY Extragonadal malformations	————————————	
Placental Aromatase	Placental estrogens	Androstenedione	Adrenal androgens	Over-viril 46,XX Maternal viril	————————————	
17 α/17,20	Cortisol Testosterone DHT	Pregnenolone 17OHPreg	Aldosterone	Under-viril 46,XY HTN Low K	↑ (s) 11-deoxy, corticosterone, progesterone ↓Testo, ACTHS↓/absent cortisol response	
17β	Testosterone DHT	Androstenedione	Estrogens	Under-viril 46,XY	Post hCG test - Andro:Testo> 20:1 ACTHS - N cortisol response	
StAR	All steroid hormones	Cholesterol	None	Under-viril 46,XY	Post hCG − ↓Testo ACTHS↓/absent cortisol response	
5α	DHT	Androstenedione	Testosterone Estrogens	Under-viril 46,XY	Post hCG − N/↑ Testo, ↑Testo:DHT Skin Fibroblast	
CAIS	AR	————————————	————————	Under-viril 46,XY	↑ MIS	
PAIS	AR	————————————	————————	Under-viril 46,XY	Post-hCG − N Testo and Testo:DHT, skin fibroblast, DNA testing ↑ MIS	

Abbreviations: s = serum; N = normal; Viril = virilizatin; 17OHPro=17-hydroxyprogesterone; 17OHPreg = 17-hyroxypregnenolone; DHEA = dehydroepiandrosterone; 11-deoxy = 11-deoxycortisol; Andro = androstenedione; Testo = testosterone; cortico = corticosterone; DHT = dihydrotestosterone; AR = androgen receptor; HTN = hypertension; ACTHS = ACTH stimulation test

mineralcorticoid replacement with 9α-fludrocortisone. The infants should also be given salt supplements with their meals.[12]

Apart from acute life-threatening issues, medical and surgical treatment will vary from case to case based on the diagnosis, the advice offered by the team of experts, and the wishes of the parents. For many patients whose gonads will never function at puberty, hormone replacement will eventually be needed in order to achieve puberty, regardless of the ultimate gender identity and assignment. Hormone replacement is carried out under the guidance of a pediatric subspecialist such as a pediatric endocrinologist, pediatric gynecologist, or a pediatric urologist. Hormone replacement often does not begin until the age when puberty would be expected (11–12 years in females and 12–13 years in males) and ideally after careful assessment of gender orientation. The current indications for hormone replacement therapy at puberty are those patients with 46,XY DSD and hypogonadism. Patients with a female gender assignment will need estrogen and those with a uterus will also eventually need a progestin. Patients with a male gender assignment will need testosterone therapy. The hormone therapy should aim to mimic the regular pace of puberty. There are a variety of hormone formulations available.[23] Hormone therapy can contribute to a growth spurt, create secondary sexual characteristics, and initiate menses (when there is a uterus and patent vagina). Similarly, the acquisition of ideal bone density relies to some degree on gonadal sex steroids or their exogenous equivalents.[1] Follow-up is crucial to assess the correct rate of secondary sex characteristic acquisition and to avoid complications of treatment such as premature closure of the epiphyses.[23]

Although there has been a wide acceptance for surgical interventions in infancy, it is suggested that most surgeries be postponed until puberty. This recommendation is due to reports that many genitoplasties and vaginoplasties performed in infancy will need to be re-done at puberty[24] to achieve satisfactory outcomes and correct complications from previous surgeries such as vaginal stenosis. Postponing the surgery would also ensure that the child could participate in decision-making and consent.[25] Another study suggests that the most important indicators for good anatomical and cosmetic results do not include timing, but that the expertise of the surgeon/surgical team and a planned one-stage surgery are the most important factors in positive long-term outcomes.[26] The potential for more complete guidelines for surgical intervention in ambiguous genitalia will depend on the completion of further long-term outcome studies.

Certain surgical procedures are less controversial. For example, in the case of CAIS patients who often orient as female, the testes will produce estrogen and allow for spontaneous puberty and feminization; therefore, many physicians/patients will opt to delay an orchidectomy until the completion of puberty. For those with a Y fragment whose gonads will never function, early removal is usually justifiable. More controversial is early feminizing genitoplasty and/or early orchidectomy performed for psychological benefit and/or to prevent malignant transformation of functioning gonads or "undesirable" androgenization at puberty.[1] In MGD where the sex of rearing is male, the current recommendation is to remove the streak gonad during early childhood. Overall, the management and treatment of a child with ambiguous genitalia is lifelong and will require the efforts of all care providers involved in the multidisciplinary team in order to achieve the best outcome and satisfaction of the patient and their family.

Gender Assignment and Psychosocial Management

Historically, an assumption was made that sex assignment/reassignment was a simple task because gender identity would be consistent with the sex of rearing.[27] This view has drastically changed, as seen in the 2004 publication by Thomas,[28] which states how challenging the 'medical' goals of treatment are in their attempt to restore 'normality' in all areas including anatomy and sexual function—not to mention the mere difficulty of defining normality in terms of human sexuality.[28] Many health care professionals are questioning what the benefit:risk ratio is when assigning a gender to an infant with ambiguous genitalia. Some papers report serious signs of dissatisfaction among patients with genital ambiguity. For example, one article looked at a group of women diagnosed with DSD and reported that, compared to a control population, they had fewer relationships, had more frequent suicidal ideation, and sought more psychological and/or psychiatric counseling for serious issues.[3] Some experts in the area feel that we should challenge the boundaries of society and push for a third sex assignment (gender yet to be determined) or no sex assignment at all.[29] Here, the child would be allowed to grow and develop without the pressure to 'behave' or 'act' like either sex; with the guidance of counselors and a strong multidisciplinary team, a gender could be chosen with the input of the child. Many regard this idea as unrealistic and the current protocols for initial gender assignment clearly state quick action as an underlying principle.[1]

There are some data available that look at specific etiologies of ambiguous genitalia and the gender identity outcome. For instance, most infants with CAH who have ambiguous genitalia are genetically female, reared as female, and have a female post-pubertal gender orientation. The fairly clear-cut potential for fertility in 46,XX CAH plays a large role in the decision to rear as female.[30] In the case of 5α-reductase deficiency, 60% of assigned females and most assigned males who virilize at puberty live their adult lives as males. Also, 25% of patients with PAIS report gender dissatisfaction no matter what gender they were assigned at birth. Most 46,XY patients with CAIS who are assigned a female gender do not experience any gender dysphoria post-puberty. Literature also suggests that all 46,XY individuals with micropenis be raised as males due to the potential for further virilization at puberty, and the ability for sexual functioning in adulthood.[1]

In general, mental health staff with experience in DSD should be a component of the multidisciplinary team from the initial meetings and should continue to be a part of the child's life well into adulthood. Should a child present with gender dysphoria around the age of puberty, the mental

health professional in contact with the child should use this opportunity to discuss feelings surrounding gender and to perform psychological evaluation. If, after thorough discussion, a child persists with the desire to change gender, the decision should be supported. Also, as children reach adolescence, their need for privacy may increase and meetings with their counselor should occasionally occur without parents. Eventually, referral to a sexual therapist may be necessary.[1] In the end, the issues that may arise will be unique to each individual and psychological support should be easily available to any patient with ambiguous genitalia from infancy to adulthood.

Summary

The purpose of this work is to focus on the classification of ambiguous genitalia which has been divided into 46,XX DSD, 46,XY DSD, and gonadal disorders. The complex nature of this condition is underlined by the numerous subclassifications found within each of these three categories. In order to diagnose a specific etiology, the basic principles of history, physical exam, and lab investigations are employed. The most recent algorithms for diagnosis emphasize the idea of choosing efficient testing methods and minimizing the harm done to the newborn. The management of a child with ambiguous genitalia will be unique and in order to provide the best care a multi-disciplinary team of health care professionals is necessary. Parents and the child should be consulted whenever possible before any decisions are made. From diagnosis and gender assignment to long-term care and quality of life, ambiguous genitalia is proving to be an intricate condition with few straightforward answers. By arming patients and their parents with as much information as possible about the details of the diagnosis, surgical and medical treatments, and potential for sexual function and fertility in the future a collective decision can be reached as to an initial sex of rearing. An important point to emphasize, however, is that no matter how well thought out a decision may be, the child may experience gender dysphoria at some point in life and may need a strong support system while making the decision to remain with the gender assigned at birth, or to take the necessary steps to undergo a change in gender.

Educational Tool

For many learners, newly acquired information and ideas are further solidified through application of knowledge. The following educational tool is meant to take the information in this article and create an interactive opportunity for the reader. As far back as 1620, educators have understood that testing (whether formally or self-administered) not only serves as a method of evaluation, but also helps with later recall and aids the learner in tailoring further studying to the areas they recognize as weak. Research also shows that an effective method for developing further comprehension and improving later recall is to answer questions at the end of a text.[31] To utilize this theory of using 'test-like events'[31] to improve learning, a teaching tool has been attached.

Fives cases have been presented. Cut out the flash cards provided and use them to create the best possible representation of that patient. Descriptive words such as low, high, normal, and abnormal should be paired with other flash cards to describe the patient in the question Example: LOW paired with Sodium and HIGH paired with potassium in the case of 21-hydroxylase deficiency CAH. An answer key has been provided with explanation. Some of the flash cards have been left empty for the purpose of the reader expanding on this educational tool if they choose. The tool has been designed for individual or small group use, but it does have great potential for team-based learning sessions.

By working through these cases, the reader will have a chance to sort through the complicated topic of ambiguous genitalia. The end goal of this activity is to further develop the initial understanding of ambiguous genitalia and provide a means to practice clinically relevant scenarios. In fulfilling this objective, we hope each learner can develop a more sensitive and thorough approach to the medical and psychosocial issues presented by a neonate with ambiguous genitalia.

Cases

1. 46,XX with 21-hydroxylase deficiency
2. Partial 5-alpha reductase deficiency
3. Normal ovary on one side and normal testes in inguinal canal on the contralateral side
4. Dysgenetic testes on one side and a streak ovary on the contralateral side
5. Partial androgen insensitivity

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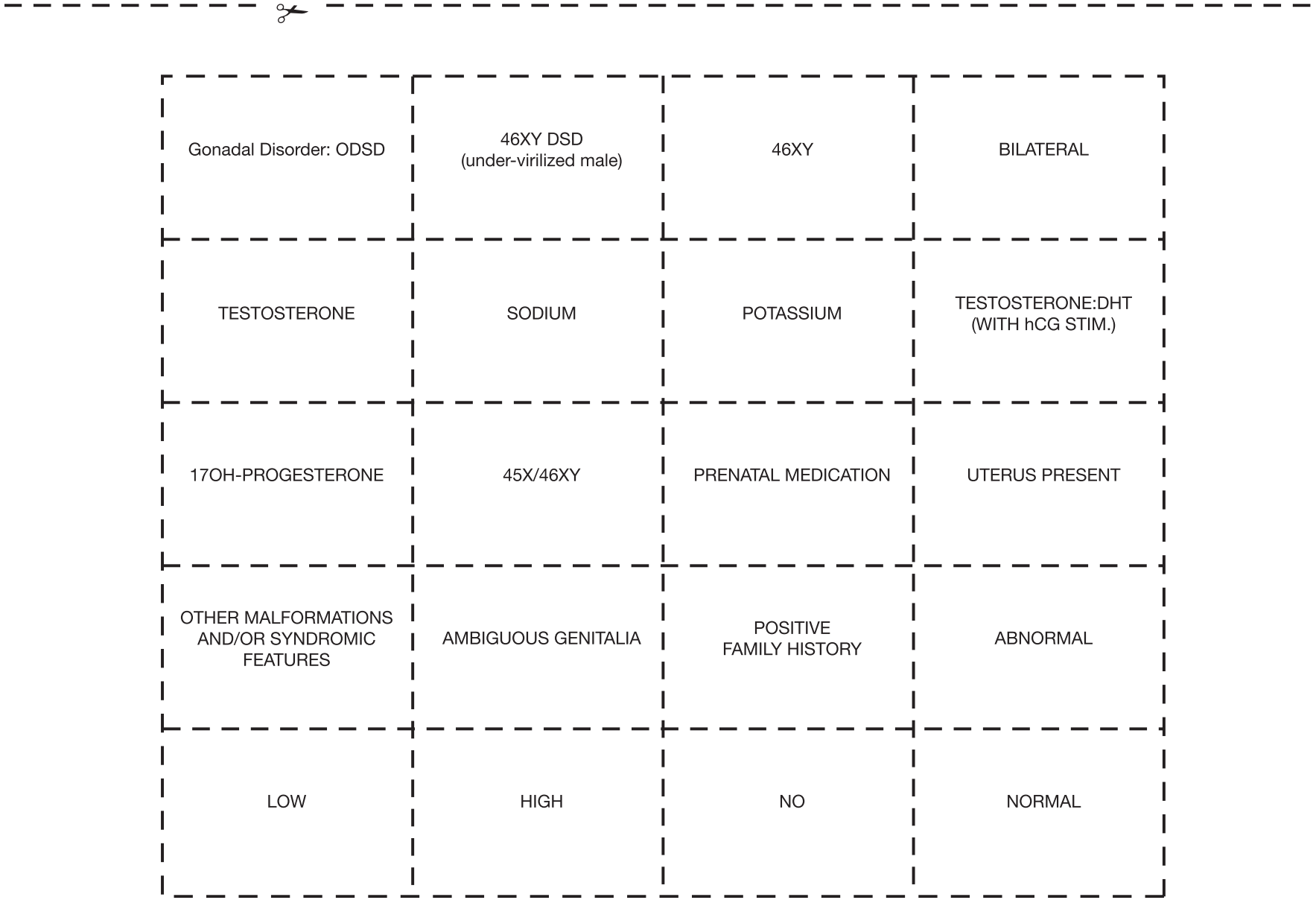
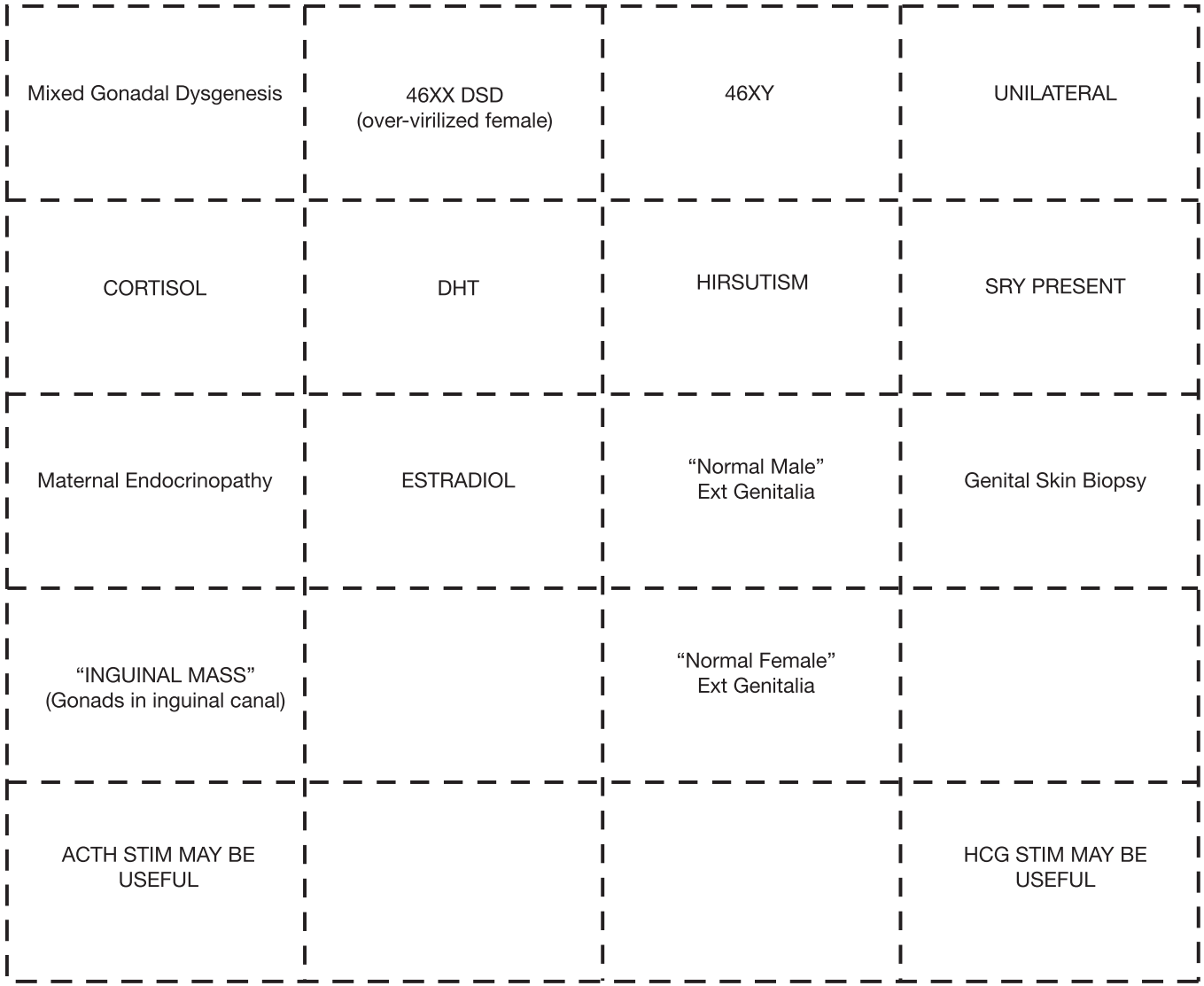

Gonadal Disorder: ODSD
46XY DSD
(under-virilized male)
46XY
BILATERAL
TESTOSTERONE
SODIUM
POTASSIUM
TESTOSTERONE:DHT
(WITH hCG STIM.)
17OH-PROGESTERONE
45X/46XY
PRENATAL MEDICATION
UTERUS PRESENT
OTHER MALFORMATIONS
AND/OR SYNDROMIC
FEATURES
AMBIGUOUS GENITALIA
POSITIVE
FAMILY HISTORY
ABNORMAL
LOW
HIGH
NO
NORMAL


Mixed Gonadal Dysgenesis
46XX DSD
(over-virilized female)
46XY
UNILATERAL
CORTISOL
DHT
HIRSUTISM
SRY PRESENT
Maternal Endocrinopathy
ESTRADIOL
“Normal Male”
Ext Genitalia
Genital Skin Biopsy
“INGUINAL MASS”
(Gonads in inguinal canal)
“Normal Female”
Ext Genitalia
ACTH STIM MAY BE
USEFUL
HCG STIM MAY BE
USEFUL

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Answers for Ambiguous Genitalia Education Tool – Clinical Cases

CASE #1 = 46 XX with 21-HYDROXYLASE DEFICIENCY

AMBIGUOUS GENITALIA POSITIVE FAMILY HISTORY (AUTOSOMAL RECESSIVE) NO PRENATAL MEDS EXPOSURE NO OTHER MALFORMATIONS UTERUS PRESENT

HIGH: 17OH-PROGESTERONE, POTASSIUM LOW: CORTISOL, SODIUM KARYOTYPE: 46 XX ACTH STIMULATION (SYNACTHEN) MAY BE USEFUL

CATEGORY: 46 XX DSD (over-virilized female)

CASE #2 = PARTIAL 5-ALPHA REDUCTASE DEFICIENCY

Answers AMBIGUOUS GENITALIA BILATERAL INGUINAL Masses (GONADS) – often, not always POSITIVE FAMILY HISTORY (AUTOSOMAL RECESSIVE) NO PRENATAL MEDS EXPOSURE NO OTHER MALFORMATIONS NO UTERUS PRESENT (no Mullerian structures)

HIGH: TESTOSTERONE (or normal male), TESTOSTERONE:DHT RATIO LOW: DHT (low for male) KARYOTYPE: 46 XY

CATEGORY: 46 XY DSD (under-virilized male)

CASE #3 = NORMAL OVARY ON ONE SIDE AND NORMAL TESTES IN INGUINAL CANAL ON THE CONTRALATERAL SIDE

AMBIGUOUS GENITALIA UNILATERAL INGUINAL HERNIA NO FAMILY HISTORY NO PRENATAL MEDS EXPOSURE NO OTHER MALFORMATIONS ABNORMAL UTERUS PRESENT (OPPOSITE SIDE TO TESTES) – OFTEN UNICORNUATE SRY PRESENT NORMAL: MOST OTHER TESTS LIKE ELECTROLYTES, HORMONES KARYOTYPE: 46 XX OFTEN BUT NOT ALWAYS

CATEGORY: GONADAL DISORDER: ODSD

CASE #4 = DYSGENETIC TESTES ON ONE SIDE AND A STREAK OVARY ON THE CONTRALATERAL SIDE

Normal Female External Genitalia (female appearance) NO PRENATAL MEDS EXPOSURE NO FAMILY HISTORY OTHER MALFORMATIONS (MANIFESTATIONS OF TURNER SYNDROME CAN BE PRESENT (EG. BRACHYDACTYLY, WEBBED NECK, SHORT STATURE), AS WELL AS URINARY TRACT ABNORMALITIES) UTERUS (OFTEN PRESENT) SRY PRESENT

KARYOTYPE: 45 X/46 XY, OFTEN BUT NOT ALWAYS

CATEGORY: MIXED GONADAL DYSGENESIS

CASE #5 = PARTIAL ANDROGEN INSENSITIVITY

AMBIGUOUS GENITALIA BILATERAL INGUINAL Masses – 50% of patients will have testes in the inguinal canal, although they can be found anywhere along the path of descent NO PRENATAL MEDS EXPOSURE NO OTHER MALFORMATIONS NO UTERUS POSTITIVE FAMILY HISTORY – x-linked recessive NORMAL: ELECTROLYTES AND HORMONE LEVELS HIGH: TESTOSTERONE (male level)

KARYOTYPE: 46 XY

CATEGORY: 46 XY DSD (undervirilized male)