Intersex Conditions

Series Editor:
Bernard Fallon, MD
Professor
Department of Urology
University of Iowa
Iowa City, IA

Contributor:
J. Christopher Austin, MD
Assistant Professor, Pediatric Urology
Department of Urology
University of Iowa
Iowa City, IA

Table of Contents

Introduction ........................................ 2
Congenital Adrenal Hyperplasia ............... 2
Mixed Gonadal Dysgenesis ..................... 8
Persistent Müllerian Duct Syndrome .......... 9
Androgen Insensitivity Syndrome ............ 10
Summary ....................................... 12
References ..................................... 12

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NOTE FROM THE PUBLISHER:
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INTRODUCTION

Ambiguous genitalia and intersex are rarely encountered conditions. Whereas normally, the birth of a baby is heralded by the announcement of the sex just after delivery, in some cases the genitalia are abnormally developed, making determination of the baby’s sex uncertain. When these rare circumstances occur, the situation can be extremely stressful and tense for the family and the evaluating team. An urgent, timely, and complete evaluation is mandatory. Hasty decisions or predictions should be avoided. Given the tremendous burden of assigning gender, a multidisciplinary team approach is crucial and should include a pediatric urologist, endocrinologist, and neonatologist. In this review, the more common intersex conditions are discussed, including those that present without ambiguous genitalia.

NORMAL EMBRYOLOGIC DEVELOPMENT OF THE REPRODUCTIVE SYSTEM

Sexual development begins with the formation of a bipotential gonad (Figure 1). Although several genes appear to play a role in this process, one of the more important genes clinically is the Wilms’ tumor suppression gene (WT1). WT1 is expressed early during development of the genitourinary tract, and defects in WT1 can cause intersex conditions (eg, Denys-Drash syndrome). Differentiation to a testis versus an ovary is dependent on genes that are found on the sex chromosomes. The Y chromosome expresses testis-determining genes, most notably SRY (sex-determining region Y-chromosome). This begins the process of differentiation from the bipotential gonad into a testis. In the absence of the expression of testis-determining genes, the gonad differentiates into an ovary. The testis contains Sertoli cells and Leydig cells. The Sertoli cells produce Müllerian inhibiting substance (MIS), which causes local regression of the ipsilateral müllerian (mesonephric) ducts, leaving only small, vestigial, remnants—the testicular appendages and the prostatic utricle. Leydig cells produce testosterone, which acts locally to stimulate development of the ipsilateral wolffian (paramesonephric) ducts, forming the seminal vesicle, vas deferens, and epididymis. Through the conversion of testosterone to dihydrotestosterone (DHT), the genital tubercle and labioscrotal folds develop into male external genitalia.

Gonadal development in the female was classically thought to follow a “default” or automatic pathway, which could only be altered by the expression of testis-determining factor. This is probably not completely correct, as there now is evidence in animal studies that ovarian-specific genes are expressed and necessary for ovarian development. The lack of MIS production allows the müllerian ducts to develop into the uterus, fallopian tube, and proximal vagina. In the absence of testosterone stimulation, the wolffian ducts regress and female external genitalia form.

Intersex is a difficult and confusing subject. If approached systematically with a basic understanding of the embryology of gonadal and genital development, however, it is much more manageable. There are 2 basic categories of intersex disorders—those that are caused by improper development of the gonads, and those that are the result of aberrant (a deficiency or excess of) activity of the hormones produced by the gonads.

CONGENITAL ADRENAL HYPERPLASIA

CASE 1 PRESENTATION

An 8-day-old baby is hospitalized for failure to thrive. The child was noted to have what appeared to be hypospadias and bilaterally undescended, nonpalpable testes. The parents were told their baby was a boy, and the child was discharged on day of life 2. At admission, the child was hypotensive. Results of serum blood chemistries are notable for hyponatremia and hyperkalemia.

• What is the differential diagnosis and appropriate evaluation for this infant?
CAUSES OF AMBIGUOUS GENITALIA

Infants with ambiguous genitalia can be divided into 4 groups based on their gonadal and phenotypic sex (Table 1). The most frequent causes of ambiguous genitalia are congenital adrenal hyperplasia (CAH) and mixed gonadal dysgenesis (MGD), which together account for nearly 75% of cases. A more extensive differential diagnosis of intersex conditions is provided in Table 2 and Table 3; the latter table lists those that present without ambiguous genitalia.

EVALUATION OF INFANTS WITH AMBIGUOUS GENITALIA

The evaluation of infants with ambiguous genitalia should include a complete history, physical examination, karyotyping, serum hormone studies, and radiographic imaging. Parents of the baby should be questioned for a family history of prior miscarriages or infant deaths, which can suggest the presence of CAH. Maternal use of hormones during or prior to pregnancy and maternal symptoms suggestive of a hormone-secreting tumor should be noted. The results of prenatal ultrasound studies and the karyotype from the amniocentesis, if performed, should be reviewed.

Physical examination should include a thorough abdominal and groin examination, searching for masses and palpating for the gonads. The genitalia evaluation should include the stretched phallic length and degree of curvature, size of the glans, urethral meatus or urogenital sinus position, and presence of labia or rugation of labioscrotal area. If gonads are palpable, their size, location, and consistency should be noted. A rectal examination should be performed with palpation in the midline anteriorly searching for a uterus and cervix. A karyotype should be obtained from peripheral blood leukocytes. Serum studies should include adrenal steroid levels, serum androgen levels, and gonadotropins. A pelvic ultrasound should reveal the presence or absence of a uterus, vagina, and possibly fallopian tubes. The gonads may be identified intra-abdominally or in the inguinal canal. Genitography performed by the retrograde injection of contrast through the perineal orifice will help define the anatomy of the urogenital sinus and show the presence of a vagina (which, unlike a utricle, should have an indentation from the cervix) as well as its location relative to the urethra and bladder neck (Figure 2).

Case 1 Evaluation

The case patient is stabilized with intravenous normal saline solution and treated with hydrocortisone and fluoroxydrolcortisone replacement. Physical examination reveals nonpalpable gonads and fusion and rugae of the labioscrotal folds (Figure 2A). The phallus measures 1.8 cm with severe ventral chordee and an orifice at the junction of the phallus and the labioscrotal folds. Pelvic ultrasonography demonstrates a uterus and ovaries bilaterally. Genitography demonstrates a long urogenital sinus prior to the confluence of the vagina and urethra (Figure 2C). The karyotype returns 46,XX. Serum hormone studies reveal a markedly elevated 17-hydroxyprogesterone level, as well as elevations of dehydroepiandrosterone (DHEA), androstenedione, and testosterone.

The markedly elevated 17-hydroxyprogesterone level and karyotype indicate that the patient is a female pseudohermaphrodite with CAH secondary to 21-hydroxylase deficiency. This case graphically illustrates why infants who appear to be males with hypospadias and have nonpalpable gonads must undergo a thorough evaluation for intersex before declaring what their sex is.

- Is it possible to be a genetic female and have a normal-appearing male phallus and scrotum without a palpable testis?

Although this is a rare and extreme presentation, there have been patients with CAH who have undergone
Intersex Conditions

neonatal circumcision. The gonads are always nonpalpa-
ble, but the degree of virilization can be so extreme that
the urethra and phallus appear completely virilized. This
again underscores the importance that a newborn who
appears to have hypospadias but has bilateral nonpalpa-
ble gonads not be presumed to be male and needs an
intersex evaluation.11

PATHOPHYSIOLOGY OF CAH

21-Hydroxylase Deficiency

A diagram of the pathway of adrenal steroidogenesis
is shown in Figure 3. While at first glance this appears
complex, one must keep in mind that 90% of cases of
CAH are due to defects in the enzyme 21-hydroxylase
(also known as P450c21).12 As shown in Figure 3, this
enzyme catalyzes the conversion of progesterone to
deoxy cortisol (DOC) and the conversion of
17-hydroxyprogesterone to 11-deoxycortisol.

CAH associated with 21-hydroxylase deficiency is
carried by a defective gene located on the short arm of
chromosome 613,14 and is inherited in an autosomal
recessive pattern. The enzymatic defects associated with
CAH may either impair or completely disrupt the activ-
ity of the enzyme. In the presence of partial enzymatic
impairment, there will be virilization without salt wast-
ing, owing to the production of mineralocorticoids. In
the complete absence of enzymatic activity, there will be
no production of mineralocorticoids, and the classic
salt-wasting form of CAH will occur. This form of CAH
accounts for approximately 75% of cases.15

Figure 3 demonstrates that progesterone, which accu-
mulates due to the defect in 21-hydroxylase, is convert-
ed to 17-hydroxyprogesterone. This, in turn, accumu-
lates in high levels due to stimulation of the adrenal
gland from lack of cortisol production. These high lev-
els increase the production of androstenedione, and—
through the accumulation of intermediate precursors—
DHEA. The presence of these weak androgens, toget-
ner with the conversion of DHEA to testosterone, result in
the virilization of the female genitalia, thereby causing
ambiguous genitalia. In males, this deficiency causes
CAH without ambiguous genitalia because the andro-
genists do not affect male genital development.

11β-Hydroxylase Deficiency

The second most common cause of ambiguous gen-
italia in females with CAH is 11β-hydroxylase deficien-
cy. This deficiency is responsible for approximately 5%
of cases of CAH. The enzyme is also known as
P450c11β,16 and the gene encoding it is found on the
long arm of chromosome 8.17 Figure 3 demonstrates
that a deficiency in the activity of 11β-hydroxylase leads
to the accumulation of 11-deoxycorticosteroid and DOC. The
important difference in these intermediaries is that
DOC has mineralocorticoid activity, and thus children
with 11β-hydroxylase deficiency have a mineralocorti-
coid excess instead of deficiency. Clinically, female
infants present with varying degrees of genital ambigu-
ity and also hypertension. The excess mineralocorticoid
results in increased sodium and water retention pro-
ducing hypertension and loss of potassium. The results
of serum chemistries are characterized by hypokalemic
alkalosis. 11β-hydroxylase deficiency is differentiated
from 21-hydroxylase deficiency by the detection in the
former of elevated levels of deoxycortisol and DOC.
Treatment of 11β-hydroxylase deficiency usually only
requires hydrocortisone treatment. Antihypertensive
treatment is occasionally required.18

Other Enzymatic Deficiencies

There are several rare mutations along the adren-
al enzymatic pathway, as well. These include defects

<p>| Table 1. Conditions Associated with Ambiguous Genitalia |
|---------------------------------|-----------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th>Category</th>
<th>Chromosomal Sex</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female pseudohermaphroditism</td>
<td>46,XX</td>
<td>Most common cause is congenital adrenal hyperplasia. Accumulation of androgens leads to virilization of genitalia.</td>
</tr>
<tr>
<td>Male pseudohermaphroditism</td>
<td>46,XY</td>
<td>Wolffian structures are usually present unless androgen resistance is very severe or androgen deficiency is complete.</td>
</tr>
<tr>
<td>Mixed gonadal dysgenesis</td>
<td>45,X/46,XY mosaic</td>
<td>Wolffian and müllerian structures are present. Etiology is improper gonad formation due to chromosomal abnormality.</td>
</tr>
<tr>
<td>True hermaphroditism</td>
<td>46,XX and 46,XX/46,XY</td>
<td>Diagnosis is based on gonadal biopsies that show both ovarian and testicular tissue.</td>
</tr>
</tbody>
</table>

4 Hospital Physician Board Review Manual
**Intersex Conditions**

**Table 2. Differential Diagnosis of Intersex Conditions with Ambiguous Genitalia**

<table>
<thead>
<tr>
<th>Normal gonadal development with abnormal genital development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female pseudohermaphroditism</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>21-hydroxylase deficiency</td>
</tr>
<tr>
<td>11β-hydroxylase deficiency</td>
</tr>
<tr>
<td>3β-hydroxysteroid dehydrogenase deficiency</td>
</tr>
<tr>
<td>Maternal androgen exposure</td>
</tr>
<tr>
<td>Maternal androgen-secreting tumor</td>
</tr>
</tbody>
</table>

| Male pseudohermaphroditism                                    |
| Partial androgen insensitivity syndrome                        |
| 5α-reductase deficiency                                        |
| Congenital adrenal hyperplasia                                 |
| 3β-hydroxysteroid dehydrogenase deficiency                    |
| 17α-hydroxylase/17,20-lyase deficiency                         |
| 20,22-desmolase deficiency                                     |
| 17β-hydroxysteroid dehydrogenase deficiency                   |
| Leydig cell aplasia                                            |
| XX sex reversal                                                |

| Abnormal sex chromosomes with abnormal gonad development      |
| Partial gonadal dysgenesis                                    |
| Mixed gonadal dysgenesis                                      |
| Dysgenetic male pseudohermaphroditism                         |
| Denys-Drash syndrome                                           |
| True hermaphroditism                                          |

**Table 3. Differential Diagnosis of Intersex Conditions with Normal-Appearing Genitalia**

| Female genitalia                                               |
| Complete androgen insensitivity syndrome                        |
| Pure gonadal dysgenesis                                         |
| Turner syndrome                                                 |
| XY gonadal dysgenesis (Swyer syndrome)                          |
| XX gonadal dysgenesis                                           |

| Male genitalia                                                 |
| Persistent müllerian duct syndrome (MIS deficiency or hernia uteri inguinalis) |
| XX sex reversal                                                 |
| Klinefelter’s syndrome (47,XXY)                                 |

MIS = müllerian-inhibiting substance.

in 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase/17,20-lyase, and side-chain cleavage enzyme. 3β-hydroxysteroid dehydrogenase deficiency causes CAH with ambiguous genitalia in both males and females, whereas deficiencies in the latter two enzymes cause CAH with ambiguous genitalia in males only, resulting from deficiencies in androgen production.14,19

**CONSIDERATIONS FOR GENDER ASSIGNMENT IN CAH**

The considerations for gender assignment in any intersex condition need to include the chromosomal sex, gonadal histology, functionality of the genitalia, potential for reproduction, risk of malignancy, and potential effects of androgen imprinting of the central nervous system. In females with CAH, the defect in cortisol metabolism results in virilization of the external genitalia, but the sex chromosomes are normal female 46,XX. The gonads are ovaries with fallopian tubes and a uterus, and the potential for fertility exists. The vagina is present, although in extreme cases it may be small. The urethra and vagina enter into a urogenital sinus that has variable length and meatal position depending on the degree of masculinization.20 The vast majority of these patients are reared as females due to these factors. The single factor that seems to point against this decision is the potential for androgen imprinting on the brain. Females with CAH have been described as acting “tomboyish,” and in studies, have had an increased incidence of homosexual preference as adults, particularly in patients who have salt wasting.21,22 In rare instances when a child being reared as male presents later in childhood, consideration should be given to continuing rearing the child as a male.

The potential role of androgen imprinting on the brain, and its importance in gender identity—the way one’s thoughts and behaviors match with one’s gender (eg, male behaviors in males)—has become a stronger consideration in gender assignment in recent years.23 It is important to realize that although functional genitalia are an important part of gender, they do not absolutely define it. The argument that gender assignment should be made solely on the basis of whether or not functional genitalia can be constructed is superficial and simplistic. Obviously, any patient with genital abnormalities may have an increased amount of anxiety as he or she sexually matures, but the prior held belief that a genetic male without a functional penis should undergo feminizing surgery and be reared as a female does not appear to be correct.
Animal studies have shown that males exposed to estrogens in utero and postnatally display female mating behaviors. Although these studies cannot be directly translated into human studies, it is apparent that there is evidence that prenatal and neonatal exposure to androgens does have some effect on human sexual behavior. This is evident in females with CAH who have tendencies to exhibit masculine behaviors. The level of exposure to androgens and the relative effects need to be considered in discussions regarding gender assignment. For example, in patients with complete androgen insensitivity, despite having male sex chromosomes, there should be no androgen effects on the brain and thus female gender assignment may be appropriate. The current understanding of the importance of androgen imprinting versus environmental factors on gender identity will hopefully be further elucidated with studies of patients who have undergone gender reassignment for deformities such as aphallia and cloacal estrophy.

**Surgical Reconstruction in the Treatment of CAH**

Currently, females with CAH are recommended to undergo feminizing surgery in infancy or early childhood. This typically consists of a vaginoplasty to create a functional vaginal introitus and provide separation of the urethra and vagina. The clitoris, which is elongated and prominent, is reduced in size. The goal of surgical reconstruction is to create functional female genitalia that will allow for intercourse and reproduction. The clitoroplasty is to prevent clitoral erections, recess

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**Figure 2.** Female pseudohermaphroditism secondary to congenital adrenal hyperplasia. (A) Photo of the patient presented in case 1 demonstrating ambiguous genitalia with clitoral enlargement, fusion of labia, and rugae of the labia majora. (B) Diagram of the anatomy of the urogenital sinus with bifurcation of the urethra and vagina. (C) Genitogram demonstrating the urogenital sinus, urethra, and vagina as diagramed in part B.
Intersex Conditions

The clitoris into the perineum, and yet maintain function to preserve sensation during sexual stimulation.24–26

The timing for performing a feminizing genitoplasty is partially surgeon and partially parental preference. It can be safely performed in infants from 3 to 6 months of age. Except in rare instances, the vaginoplasty can be performed using an inverted U-shaped flap from the perineum. The patient is positioned in the dorsal lithotomy position and given intravenous antibiotics and hydrocortisone. Pan-endoscopy is performed, in which the length of the urogenital sinus, the site of divergence of the urethra and vagina, and the location of the external sphincter are noted. A Fogarty balloon may be placed in the vagina to mark it. The skin and urogenital sinus are then incised in the midline until the vagina is encountered. The lateral and posterior walls of the vagina are freed. The apex of the U-flap is then sutured to the posterior wall of the vagina. The vagina is then sutured to the skin edges laterally. The clitoroplasty involves degloving the clitoris and making lateral corporotomies to remove the spongiosal tissue to prevent erections. The dorsal neurovascular bundle should be preserved. The clitoris is recessed close to the pubis and hooded. The mucosal strip is left in place and the excess clitoral skin is split dorsally and used to create labia minora. A Foley catheter is left overnight and the incisions are covered with petroleum jelly gauze. There is no need for vaginal dilations, a vaginal pack, or vaginal stent. An alternative approach for when the distance from the vagina to the perineum is too far has been to use the excess clitoral skin to create a tube, which is used as an interposition flap between the vagina and perineum.

The surgical reconstruction for CAH has been criticized as being harmful and ineffective by organizations such as the North American Intersex Society.27 They suggest that any reconstructive surgery should be the decision of the individual patient and not that of parents or physicians. The long-term outcomes for vaginoplasties for CAH are not known and there may be significant problems that would not manifest until the child is pubertal. A recent retrospective review showed a high incidence of stenosis at the introitus.28 The issue of reconstructive surgery in the female with CAH will remain controversial. The North American Task Force on Intersex has been formed in response to these concerns. Through the cooperation of physicians and patients with intersex conditions, the task force’s goal will be to investigate outcomes and aid in defining optimal therapy.

Figure 3. Pathways for steroid synthesis in the adrenal cortex. The dotted horizontal lines indicate the site of activity for the 2 most common defects causing congenital adrenal hyperplasia with ambiguous genitalia in females: 21-hydroxylase and 11β-hydroxylase deficiencies.
ANTENATAL TREATMENT OF CAH

Because CAH is a genetically transmitted disease, parents of a child with CAH should be warned of the possibility of subsequent offspring being affected. The disease is autosomal recessive, and thus if both parents are heterozygous carriers, each child has a 25% chance of having the disease and a 50% chance of being a carrier. The risk of bearing a female with virilization would be 12.5%.

There is the potential for in utero therapy for 21-hydroxylase deficiency with steroid replacement. Treatment is initiated with oral dexamethasone beginning at the fifth week of gestation. Genetic testing for CAH is performed using tissue obtained by chorionic villus sampling at 9 to 11 weeks’ gestation or amniocentesis at 15 to 18 weeks’ gestation. If the karyotype is female and CAH is present, treatment continues. Although experience with this approach has been limited, there appears to be minimal virilization of the fetus with no obvious adverse effects. Of concern, however, is that the great majority of fetuses will be treated unnecessarily.

MIXED GONADAL DYSGENESIS

CASE 2 PRESENTATION

A 1-month-old male is referred for evaluation of hypospadias and cryptorchidism. His physical examination reveals penoscrotal hypospadias with severe chordee. The stretched penile length is 2.5 cm. The left testicle is descended into a well developed, rugated scrotum. The right testis is not palpable. The child is felt to have hypospadias and right undescended testicle. No further work-up is performed.

At 6 months of age the child undergoes right inguinal exploration, which demonstrates the absence of a testis or cord structures. Abdominal exploration reveals absence of an obvious testis and vas deferens, but the presence of structures that appear to be a uterus, fallopian tube, and streak gonad. The structures are resected and confirmed histologically. The left testis is biopsied longitudinally and showed seminiferous tubules with depleted germ cells. A karyotype returns with a mosaic pattern of 45,X/46,XY.

• What is the diagnosis of this patient?
• What is the cause of this disorder?

The mosaic karyotype and presence of a streak gonad with associated ipsilateral müllerian structures in this patient indicate that his condition is caused by abnormal gonad formation. The diagnosis is mixed gonadal dysgenesis (MGD), which is characterized by the presence of a testis on one side and a dysgenetic gonad on the other side. This diagnosis spans a wide spectrum of genital ambiguity, from what appears to be a male with hypospadias to a mildly virilized female.

PATHOGENESIS

The most common karyotype of patients with MGD is 45,X/46,XY. The chromosomal abnormality leads to the formation of a dysgenetic, streak, or absent gonad. This, in turn, results in a lack of production of müllerian-inhibiting substance (MIS) ipsilaterally, leading to persistence of the müllerian structures. All of those affected, therefore, have a uterus and fallopian tube present. Interestingly, when detected prenatally, the mosaic karyotypes such as 45,X/46,XY karyotype are only rarely associated with a genital abnormality. However, 20% of patients had either mental retardation or autism.

MANAGEMENT

Severely undervirilized patients with MGD have been raised as female, whereas those who are more virilized are typically raised as male. There is an increased risk of gonadoblastoma in patients with MGD (estimated 15%–30%). Tumors may occur in either testis, and gonadoblastoma may progress to a germ cell tumor. Due to the high risk of tumor formation, all testes should be brought to the scrotum if they are undescended. Streak and dysgenetic testes should be removed. The management of an apparently normal contralateral testis is controversial. Recognizing the increased risk of tumor formation, some have suggested that biopsy and sometimes serial biopsy be performed to exclude carcinoma in situ or a germ cell tumor. A more liberal management plan would be close observation and serial physical examinations.

OTHER SYNDROMES OF ABNORMAL GONADAL DEVELOPMENT

Pure Gonadal Dysgenesis

Pure gonadal dysgenesis is the abnormal development of both gonads. As a result, hormone production fails and the genitals therefore feminize, regardless of the chromosomal sex. For this reason, unlike mixed gonadal dysgenesis, pure gonadal dysgenesis does not produce ambiguous genitalia.

The classic form of pure gonadal dysgenesis is Turner syndrome (45,X or 45,X/46,XX). These patients characteristically have short stature, webbed neck, and a shield chest. They often present at puberty with
Intersex Conditions

amenorrhea. Associated anomalies include horseshoe kidneys, coarctation of the aorta, and aortic valvular defects. The gonads are streak bilaterally. There is no need for resection of the streak gonads, as they do not carry an increased risk of malignancy. Infertility is the rule in Turner syndrome, with extremely rare exceptions.35

Two other forms of pure gonadal dysgenesis exist: 46,XX and 46,XY. In 46,XX gonadal dysgenesis, the gonads are streak bilaterally. Phenotypically, patients have a normal female appearance with the absence of the stigmata of Turner syndrome. As with Turner syndrome, the gonads can be left in place and do not carry a risk of increased malignancy.

Gonadal dysgenesis with the 46,XY karyotype, on the other hand, does carry an increased risk of gonadal tumors. The clinical characteristics are female phenotype. Those affected either present at birth owing to discordance with the karyotype or at puberty owing to amenorrhea. Serum testosterone levels are castrate and serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are elevated.36 If left untreated until adulthood, there is an approximately 60% risk of tumor formation in the gonad. The most common tumor is gonadoblastoma, but others, including dysgerminomas and germ cell tumors, can occur. Occasionally, precocious puberty from a hormone-secreting tumor occurs.

Because of the high risk of malignancy, the streak gonads in patients with XY dysgenesis should be removed.37 The basic rule is that dysgenetic or streak (ie, abnormal) gonads associated with a Y chromosome have a high risk of malignant transformation, whereas those associated with only X chromosomes do not.

True Hermaphroditism

A patient with true hermaphroditism has gonadal tissue from both sexes (ovarian and testicular) as opposed to only testicular gonadal tissue in MGD. Histologically, a streak gonad shows ovarian stroma that occasionally contains primordial follicles. In contrast, ovarian tissue should demonstrate mature follicles. Thus, a streak gonad can sometimes be misinterpreted as ovarian, leading to misdiagnosis.37

The gonads of persons with true hermaphroditism may be any combination of ovary, testis, and ovotestis. The most common pattern is ovary/ovotestis (35%). The most common karyotype is 46,XX, which occurs in 70% of patients and is the typical karyotype in patients of African descent.37–39 One or more of the gonads are often palpable. The müllerian or wolffian structures tend to parallel the ipsilateral gonad type. Ovotestes are usually polar and are localized to opposite poles of the gonad (typically superior and inferior). Thus it is important when performing a biopsy of the gonad to take a longitudinal biopsy to evaluate both poles. Persons with true hermaphroditism who have a normal uterus and fallopian tubes are capable of reproduction.

The management after diagnosis involves removal of the inappropriate gonadal tissue for the gender of rearing, which is determined by the gonadal tissue types and degree of virilization or feminization. An ovotestis may be treated by partial resection, with removal of the ovarian or testicular tissue depending on the sex of rearing.41

Persistent Müllerian Duct Syndrome

CASE 3 PRESENTATION

A 14-month-old male is referred for evaluation of bilaterally undescended testes. The physical examination is remarkable for a normal penis and bilaterally nonpalpable testes. The child undergoes bilateral groin explorations and the testes are found intra-abdominally on both sides. During the exploration, additional structures are found associated with the testes on each side. The groin exploration is converted to a laparotomy. The associated structures and testes are shown in Figure 4.

- What is the diagnosis of this patient?
- How should this patient be evaluated?

PATHOGENESIS AND CLINICAL PRESENTATION

Figure 4 shows the presence of testes that are closely associated with müllerian structures—in this case, fallopian tubes and a uterus. Persistent müllerian duct syndrome, also known as hernia uteri inguinalis, is characterized by the presence of testes and the persistence of müllerian structures. There are 2 known etiologies: a deficiency of MIS production or activity, and a defect in the MIS receptor.43 Both types are inherited in an autosomal recessive pattern. Owing to a failure of müllerian regression in these cases, development of a uterus, fallopian tubes, and proximal vagina occurs.

Physical findings characteristic of this syndrome are undescended testes and a normal, male phallus.42 Although rare, these cases typically present unexpectedly when a routine orchidopexy is planned. One or both testes may be undescended. The location of the testes varies and they may or may not be palpable. The testes produce normal levels of testosterone and
Intersex Conditions

**EVALUATION AND MANAGEMENT**

When müllerian structures are encountered during surgical exploration, blood should be sent for karyotype and MIS level. Consideration should be given to performing a testis biopsy and replacing the testis into the abdomen and awaiting the results of the intersex workup before proceeding with orchidopexy. Infertility is the rule with these patients, with rare exceptions. There have been several case reports of testicular tumors in these testes. Therefore, if the testis cannot be brought down to a scrotal location, consideration should be given to excision of the testis.

- What are the anatomical considerations for orchidopexy in patients with persistent müllerian duct syndrome?

  The position of the undescended testes may be inguinal or intra-abdominal. Persistent müllerian duct syndrome should be suspected when transverse testicular ectopia is encountered. These cases can represent a formidable surgical challenge to bring the testes to a scrotal location. This is primarily due to the intimate association of the fallopian tube and cord structures, which hinders the dissection and lengthening of the vessels for scrotal placement. For this reason, dissection of the cord structures must be done meticulously.

  If the testes are significantly tethered by the müllerian structures, consideration should be given to performing a partial or total hysterectomy. Also, by dividing the uterus in the midline or resecting part of the myometrium, enough length can be gained to bring the testes to a scrotal location. If the testicular vessels are too short and the testis cannot be brought down to the scrotum, the vessels can be divided and a 1- or 2-stage Fowler-Stephens orchidopexy performed.

  Currently, many patients with a nonpalpable testis are managed with laparoscopic orchidopexy instead of groin exploration. The findings and surgical treatment of persistent müllerian duct syndrome can be managed laparoscopically as well, using the same surgical strategies. Whether or not to proceed laparoscopically depends on the surgeon’s level of skill and experience.

**ANDROGEN INSENSITIVITY SYNDROME**

**CASE 4 PRESENTATION**

A 1-day-old newborn is referred for consultation. The child was born to a 38-year-old woman who underwent prenatal screening, including amniocentesis. The karyotype was 46,XY. The genitals could not be identified during prenatal ultrasound examination, and the parents were reassured that this was not uncommon and that their fetus was male based on the karyotype. At birth, the infant had what appeared to be completely normal female external genitalia. The physical examination confirms normal-appearing female external genitalia.

- What is the differential diagnosis of this infant?
- How should this infant be evaluated?

**Figure 4.** Intraoperative photograph of the patient presented in case 3 demonstrating bilateral intra-abdominal testes (held by traction sutures) and the associated müllerian structures. Note that both sides coalesce in the midline, where the uterus is located.
The broad differential diagnosis of an infant with 46,XY pseudohermaphroditism with severely feminized genitalia should include CAH 3β- and 17β-hydroxysteroid dehydrogenase deficiency (failure of testosterone production by the testes), androgen insensitivity (partial and complete), 5α-reductase deficiency, and Leydig cell aplasia.

EVALUATION OF CASE PATIENT

The evaluation of this patient should include a thorough physical examination, including a careful examination of the groin palpating for gonads and a rectal examination to palpate for a uterus and cervix. A pelvic ultrasonogram should be obtained to confirm the presence or absence of a uterus and ovaries. A repeat karyotype should be obtained, as well as serum LH, FSH, testosterone, DHT, androstenedione, DHEA, and adrenal steroid levels.

In the case of this patient, the repeat karyotype is 46,XY and the testosterone level is normal. The ultrasound examination does not identify a uterus or ovaries. The normal testosterone level rules out CAH and 17β-hydroxysteroid dehydrogenase deficiency—failure of virilization in these conditions is caused by very low to undetectable levels of testosterone. The absence of genital ambiguity rules out partial androgen insensitivity.

The difficulty in this case is to differentiate 5α-reductase deficiency from complete androgen insensitivity syndrome (CAIS). To differentiate these 2 disorders, an HCG stimulation test or DNA sequencing of the 5α-reductase gene (SRD5A2) can be performed. In patients with 5α-reductase deficiency, the HCG stimulation test should demonstrate an elevated testosterone/DHT ratio; this elevated ratio results from the production of testosterone from the testes and the failure in the presence of a 5α-reductase deficiency to convert the testosterone to DHT.59,60 The best known cohort of patients with 5α-reductase deficiency was studied in the Dominican Republic.51 The infants were reared as females and would virilize at puberty, presumably due to peripheral conversion of testosterone to DHT. Gender conversion was the result of gonadectomy performed at puberty. The testes produce high levels of testosterone, which is converted to estrogen by peripheral aromatase activity. The estrogen leads to the development of female secondary sex characteristics. In patients who undergo postpubertal gonadectomy, estrogen replacement therapy should be initiated following the procedure. The advantages of early gonadectomy are the avoidance of a secondary procedure, less psychological trauma in a young child versus a teenager, and a lower risk of future complications.

PATHOGENESIS AND CLINICAL PRESENTATION OF CAIS

Both complete and partial AIS either result from de novo mutations in the androgen receptor gene or are inherited in an X-linked recessive pattern.56 CAIS has been referred to as testicular feminization syndrome and Morris syndrome. In patients with CAIS, the testes produce testosterone but there is no response, owing to abnormalities of the androgen receptor. Therefore, the Wolffian structures involute. Because MIS is produced, the müllerian structures also regress. The absence of DHT response on the external genitalia leads to the formation of a blind-ending vagina and a female introitus. The gonads typically are intra-abdominal testes with absent spermatogenesis.53 All patients are infertile. Because of the resistance to androgen, androgen imprinting in the brain does not occur, and thus patients with CAIS strongly associate with female gender identity.54

Patients with CAIS classically present either as prepubertal females with testes discovered during inguinal hernia repair or with primary amenorrhea during puberty.54 These patients typically have tall stature, with normal breast development but sparse pubic hair. This diagnosis should be kept in mind when treating a female with bilateral inguinal hernias. In patients with CAIS, vaginoscopy will reveal a blind-ending vagina with an absent cervix. Prenatal screening (amniocentesis and chorionic villus sampling) has resulted in the identification of infants with a discordant karyotype (46,XY karyotype with phenotypically normal female genitalia).55

MANAGEMENT OF CAIS

- What is the appropriate timing of gonadectomy in patients with CAIS?

The intra-abdominal testes have an increased risk of malignant transformation and should be removed. Pathologic findings typically found in the gonads of patients with CAIS include increased numbers of Leydig cells and seminiferous tubules without spermatogenesis.53 The timing of gonad removal remains controversial, however. The classic teaching has been that the gonads should be left in place until after puberty. The testes produce high levels of testosterone, which is converted to estrogen by peripheral aromatase activity. The estrogen leads to the development of female secondary sex characteristics. In patients who undergo postpubertal gonadectomy, estrogen replacement therapy should be initiated following the procedure. The advantages of early gonadectomy are the avoidance of a secondary procedure, less psychological trauma in a young child versus a teenager, and a lower risk of future complications.
Intersex Conditions

risk of development of malignancy. The disadvantage is that it makes hormone replacement more complex during and before puberty.

If a child with a known diagnosis of CAIS develops inguinal hernias, gonadectomy can be performed at the time of hernia repair. This should be preceded by a thorough discussion between the parents and the child’s pediatric endocrinologist. Gonadectomy in the absence of hernias can be done laparoscopically with minimal morbidity.46

OVERVIEW OF THE SPECTRUM OF ANDROGEN INSENSITIVITY SYNDROME

• What are the differences between partial and complete AIS?

AIS comprises a spectrum of disorders that occur in genetic males ranging from a normal female phenotype to a normal male phenotype. Patients present with infertility and gynecomastia. The many phenotypes have been referred to as various syndromes, including Lubs, Reifenstein, Gilbert-Dreyfus, and Rosewater,57 but in actuality, these syndromes are differing presentations of the same disorder. More recently, the disorder has been classified by numbers ranging from AIS 1 to AIS 5. AIS 1 indicates a phenotypic male whereas AIS 5 indicates a phenotypic female. AIS 3 is ambiguous. AIS 2 and AIS 4 have more masculine or feminine characteristics, respectively.58

Patients with partial AIS have varying responses to exogenous testosterone administration. In patients with ambiguous genitalia, the sex of rearing is often determined by the response to testosterone. Patients who respond to exogenous testosterone with phallic growth are reared as males, whereas those who do not respond are often reared as females. Those raised as males will need to undergo orchidopexy and hypospadias repair (Figure 5). Interestingly, patients from the same family with identical mutations in the androgen receptor gene can have significantly different phenotypes. This may be due in some cases to differences in the activity of the 5α-reductase gene, which, if increased, would produce DHT with its higher affinity for the androgen receptor and produce a greater degree of virilization.59

SUMMARY

Ambiguous genitalia and intersex represent a wide range of disorders. The most common are CAH and MGD. A basic understanding of the development of the reproductive tract aids in the comprehension of these disorders. Intersex conditions are caused either by abnormal gonadal development or by disorders of the hormones responsible for sexual differentiation.

REFERENCES


**Figure 5.** Photographs of a patient with partial androgen insensitivity prior to hypospadias repair. Patient has been previously treated with bilateral orchidopexy and testosterone. He responded to testosterone treatment with favorable phallic growth. Note sparse pubic hair from testosterone stimulation. (A) Bifid scrotum and penis with severe chordee. (B) Perineal urethral meatus with an intact urethral plate.
