A Practical Approach to Intersex

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When a child is born, the first question often asked, “Is it a girl or a boy?” Society is organized around the distinction of the sexes and our treatment of the infant from day 1 is influenced by the assigned gender. Huge societal pressures, both overt and unconscious, come to bear on the child and family based on this designation. This is not a modern 21st century phenomenon. Nearly all societies throughout history have been captivated by the psychological and physical mysteries of reproduction and the different roles of the sexes. The physical appearance of the genitalia was and remains a prime concern to societies. Surrounded by mystery, religion, and societal identity, male and female genitalia surgery remains a cultural phenomenon sparked with emotion. How much more confusing when altered anatomy exists!

Today, with ambiguous genitalia, we have biochemical insight that provides a scientific explanation and surgical expertise that allows us to define physical “normalcy.” Yet, despite our increased understanding of the biochemical factors involved in the regulation of sexual differentiation, the practical management of ambiguous genitalia remains fraught with uncertainties. We are only beginning to understand the factors behind sexual identity and behavior, and how this may be independent of physical appearance. As both male and female genitalia arise from a common physical structure, ambiguity arises out of incomplete or altered differentiation. There are a number of different published classification systems categorizing the different types of patients with ambiguous genitalia. A basic background to the phenomenon of ambiguous genitalia is provided, and the biochemical steps which lead to altered external genitalia, and surgical options are reviewed. The controversies involved in the modern care of these patients are also discussed.

Gonadal Differentiation

Traditional teaching is that chromosomal sex predetermines gonadal sex, which determines phenotypic sex. It is in the basis of this concept that the development of the genitalia will be explored. Figure 1 shows an overview of the hormonal stimuli that lead to genital development. It has been appreciated since the 1950s that the genetic material for male differentiation is located on the Y chromosome (Hughes, 2002). Genital development is a stepwise process that is determined on both sequence and timing starting with the presence or absence of the testis-determining factor on the Y chromosome, in the SRY gene region.

Starting about the 5th week of development, the primary germ cells migrate from the yolk sac to the retroperitoneum where they form a germinal epithelium referred to as the urogenital ridge. Dependent upon the XY or XX chromosomal material, gonadal induction at the 6th week leads to selected germ cell growth into the underlying mesenchyme. This gives rise to primary sex cords and seminiferous tubules in the testis during the 7th week or the primary follicles in the ovary during the 10th week (Hughes, 2002). Two X chromosomes are needed for normal ovarian differentiation.

Genitalia Differentiation

In both males and females, two sets of genital ducts form: the...
The Wolffian (mesonephric) duct, which goes on to form the male genital ducts (vas deferens, seminal vesicles, and epididymis), and the Müllerian duct, which forms the female genital ducts (fallopian tubes, uterus, and proximal vagina). The Wolffian duct forms initially as the drainage system of the primitive mesonephros, with the Müllerian duct forming concurrently along the genital ridge during the 6th week of life. The presence of Sertoli cells in the male-differentiated gonad produces Müllerian Inhibiting Substance (MIS). This is a paracrine substance leading to ipsilateral regression of the Müllerian duct. In the absence of MIS, the Müllerian duct will autonomously develop along female gender lines. In the absence of testosterone, the external genitalia remain phenotypically female.

At approximately the same time as MIS secretion, the Leydig cells of the testis start to secrete testosterone. This also acts as a paracrine (locally acting) hormone-stimulating ipsilateral Wolffian duct development. Between the 9th and 12th week of gestation, if testosterone is present, the ambiguous external genitalia undergo male differentiation. The external genitalia require the conversion of testosterone to the metabolically active dihydrotestosterone (DHT) by the microsomal enzyme 5-reductase. DHT leads to the midline fusion of the labioscrotal folds creating the scrotum, urethra, and male phallus. If labioscrotal fusion has not occurred by the 12th week, further androgen exposure will lead to phallic growth but will not result in further midline fusion. In the final trimester, under the influence of MIS, testosterone, mechanical pressures, and neurologic mediation, the testicles descend into the scrotum (Pajkrt & Chitty, 2004). Figure 1 shows where problems with gonadal and genital differentiation can arise. Starting in the upper left-hand, if the testis determining factor (TDF) is present, a testis will form; if absent and two X chromosomes are present, an ovary will form. If TDF is absent from a Y chromosomal fetus, if there is a solitary X or Y chromosome, or if mixtures of XX and XY cells co-exist in the same individual (chromosomal mosaicism), then a problem in gonadal differentiation is possible. In this way, chromosomal sex determines gonadal sex.

Assuming no problems in gonadal differentiation, hormonal factors at both the local paracrine and global endocrine level come into play for male internal and external genital.

**Figure 1. Gonadal and Genital Differentiation**

<table>
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<tr>
<th>Undifferentiated gonad and female phenotype</th>
<th>Testis</th>
<th>Ovary</th>
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<tbody>
<tr>
<td>XX</td>
<td>Y (TDF)</td>
<td>X</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Testosterone</td>
<td>Testosterone</td>
</tr>
<tr>
<td></td>
<td>MIS</td>
<td>MIS</td>
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<tr>
<td></td>
<td>Stimulates Wolffian duct*</td>
<td>Stimulates Wolffian duct*</td>
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<td></td>
<td>Virilization external genitalia**</td>
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<td>Regression Müllerian ducts</td>
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<th>Persistent Müllerian ducts</th>
<th>Virilization external genitalia</th>
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**TDF = Testis Determining Factor, MIS = Müllerian Inhibiting Substance**
development. This is what is meant by gonadal sex determining phenotypic sex. Female genital development is passive. If an ovary is present but there is androgen stimulation, either in the form of exogenous androgens from the mother or endogenous androgens from an adrenal source, then the female genitalia will undergo virilization. If a testis is present, MIS leads to apoptosis of the Müllerian ducts, testosterone leads to development of the Wolffian ducts, and conversion of testosterone to DHT leads to external genitalia differentiation. If the Sertoli cells fail to secrete MIS, Müllerian ductal structure will remain, even in the presence of normal testosterone production by the Leydig cells. If the Leydig cells fail to produce testosterone, if there is a testosterone receptor deficiency, or if there is a deficiency of 5-reductase, there may be varying levels of undervirilization.

**Diagnostic Evaluation**

The spectrum of ambiguous genitalia can pose a diagnostic dilemma. There are strong pressures to provide a rapid gender determination with limited information. It is a challenge to the clinician’s skill to impress upon the parents the need to complete a full biochemical, anatomic, and multidisciplinary evaluation before rushing to an arbitrary gender assignment. Equally important to impress upon the parents is the fact that the gender chosen by the parents and health care providers may not be the same gender later chosen by the patient. The goal is to determine the underlying metabolic abnormality and to assign a gender most compatible with the future sexual satisfaction of the patient. Understanding the above discussion on the embryogenesis of the gonads and genitalia can narrow the possibilities.

A number of factors go into gender determination, starting with a history and physical. Important points of history include any maternal exposure to endogenous or exogenous androgens. A family history is also important, specifically a family history of gonadal defects, prior miscarriages, or early infant deaths. Physical examination may reveal palpable gonads, which are nearly always testes. The degree of virilization is important in determining cause as well as treatment strategies. The length and girth of the phallus is important in determining if a functional penis is present. It is vital to assess the electrolyte status of the newborn, as many forms of congenital adrenal hyperplasia associated with ambiguous genitalia are associated with mineralocorticoid over or undersecretion. Dark pigmentation of the genitalia and areola may indicate overproduction of melanocyte-stimulating hormone from adrenocorticotropic hormone (ACTH) and signs of dehydration may be indicative of salt wasting. Chromosomal determination is important but not an absolute determinant of gender. Chromosomal analysis may take several days to obtain. Pending these results, chromatin stains can help to determine the presence or absence of a second X chromosome and fluorescent Y stains can help identify the Y chromosome. Some patients may exhibit asymmetrical staining suggesting genetic mosaicism (Ogilvy-Stuart & Brain, 2004). The internal genitalia are important in determining potential for future fertility, just as the adequacy of the external genitalia are important to assess prior to male gender assignment. Finally, despite all present day tests and examinations, it is impossible to determine in all patients which gender the patient will prefer later in life. We know little about the effects of hormonal imprinting on the fetal brain and can not predict all of the socialization pressure of the child with corrected and uncorrected genital malformations.

**Specific Disorders of Ambiguous Genitalia**

Female pseudohermaphroditism. By definition, a female pseudohermaphrodite is a genetic female with ovaries but virilized external genitalia. This may arise from either endogenous production of androgens or exogenous androgen exposure such as from a maternal source. The most common variant of classic ambiguous genitalia is the female pseudohermaphrodite secondary to congenital adrenal hyperplasia. Figure 2 shows the pathways of corticosteroid biosynthesis that are involved in congenital adrenal hyperplasia. The most common defect that leads to ambiguous genitalia and female pseudohermaphroditism is a defect in the enzyme 21-hydroxylase. Other enzymatic defects in the process may also lead to both male and female pseudohermaphroditism. Starting in the upper left hand corner, cholesterol is synthesized in the adrenal into androgens, mineralocorticoids, and cortisol. Cortisol levels drive the process through feedback loops in the hypothalamus and pituitary. If cortisol levels are low because of an enzymatic defect preventing its production, such as when there is a 21-hydroxylase deficiency, then the pituitary responds by increased ACTH secretion leading to further stimulation of the system and a buildup of the precursor molecules. Such a shift leads to overproduction of androgens leading to virilization and underproduction of the mineralocorticoids leading to salt wasting.

The elevation of serum levels of precursors also provides a means of diagnosis. Both serum and urinary levels of 17-hydroxyprogesterone will be elevated in
patients with 21-hydroxylase deficiency and 17-hydroxyprogrenenolone will be elevated in patients with 3ß-steroid dehydrogenase defect. Also associated with male pseudohermaphrodites may be 3ß-steroid dehydrogenase deficiency. Patients with the uncommon 11ß-hydroxylase deficiency will have both virilism and hypertension from the elevation of androgens and the elevation of the mineralocorticoid 11-deoxycorticosterone.

Congenital adrenal hyperplasia is alone among the causes of ambiguous genitalia as being potentially life threatening in the newborn, because of the potential for mineralocorticoid deficiency leading to hyponatremia, hyperkalemia, dehydration, and circulatory collapse during the 2nd week of life.

Male pseudohermaphroditism. A male pseudohermaphrodite has a 46XY karyotype but deficient masculinization of the external genitalia. There are three basic mechanisms of undervirilism that lead to male pseudohermaphroditism. It may occur through inadequate testosterone production, inadequate testosterone metabolism, or through an androgen receptor defect.

**Figure 2.** Corticosteroid Biosynthesis and its Relationship to Congenital Adrenal Hyperplasia

![Pathway of biosynthesis of corticosteroids.](image-url)
Inadequate testosterone production may occur from Leydig cell deficiency. This may be from testicular hypoplasia or absence. Testicular absence is thought to occur most commonly as testicular regression rather than primary agenesis. It is surmised that a fetal mishap such as bilateral prenatal torsion leads to loss of testicular tissue. More commonly, inadequate production is due to an inborn error in androgen biosynthesis. Figure 2 shows certain enzymatic defects in congenital adrenal hyperplasia that may lead to underproduction of cortisol and mineralocorticoids; in a similar manner, different enzymatic blocks may cause underproduction of androgens. Location of the block will influence mineralocorticoid under or overproduction. Patients may be hypertensive from salt retention induced from excessive mineralocorticoids. This may be the presenting finding in females. In the male, they too may be hypertensive, but they tend to present earlier due to undervirilism. Examples of enzymatic defects which may lead to male pseudohermaphroditism are 3β-hydroxysteroid dehydrogenase, 17-hydroxylase, 17,20 desmolase, and 17β-hydroxysteroid dehydrogenase deficiencies. The level of undervirilism will vary in each of these conditions depending on the degree of enzymatic block, level of the block, and time of diagnosis. Some conditions such as 17β-hydroxysteroid dehydrogenase deficiency are initially associated with nearly complete lack of virilization until puberty when they may present as severe late virilization in a phenotypic female (Forest, 2001).

Male pseudohermaphroditism from inadequate testosterone metabolism is secondary to 5α-reductase deficiency. Testosterone production is normal but they are unable to produce DHT, which is responsible for virilization of the external genitalia. These patients have a 46XY karyotype, regression of müllerian ducts, normal wolffian duct structures, hypoplastic prostates, and varying degrees of undervirilism of the external genitalia. The typical patient is a phenotypic female at birth with normal male internal genitalia. Most are raised as females. At puberty, they will exhibit virilization, phallic growth, testicular descent, and deepening of the voice. Because brain receptors respond to testosterone, not DHT, these patients may have a male gender identity (Forest, 2001).

Androgen receptor defects may be total or incomplete. The former condition is commonly referred to as testicular feminization syndrome. These patients often present at puberty as phenotypic females with amenorrhea. Or, they may present earlier as a phenotypic female with an inguinal hernia containing a palpable gonad, which turns out to be a testis. Often these patients have a normal female habitus, breast development, sparse pubic hair, and a short blind-ending vagina, which may be adequate for intercourse. They are sterile, but otherwise physically and mentally female and are always reared as such. Because of the risk of gonadal tumors, testes should be removed.

Patients with partial androgen insensitivity will present with incomplete masculinization of varying degree. These patients may have a small phallus with proximal hypospadias, a bifid scrotum with penoscrotal transposition, and at times a small blind-ending vaginal pouch. More severe forms will resemble an overvirilized female more than an undervirilized male. Management is individualized to the patient. Because there is minimal response to testosterone, androgen treatment may be unsatisfactory to produce adequate phallic growth. Consideration should be given towards female gender assignment in those patients thought to have an inadequate phallus.

A rare disorder called hermaphroditism is seen with inadequate Sertoli cell production of MIS, leading to persistent müllerian ductal structures. These patients are normally masculinized; however, at the time of hernia or correction of undescended testis, a uterus and fallopian tube may be found. Treatment includes orchidopexy and hysterectomy with care being taken to preserve the testicular blood supply, which may be related to the uterus and fallopian tube.

Pure gonadal dysgenesis. Pure gonadal dysgenesis refers to a primary defect in gonadal formation. It may occur in patients with both 46XX and 46XY karyotype. Females with 46XX will have a normal stature, sexual infantilism, and bilateral streak gonads. They will often present with delayed puberty and amenorrhea and will be sterile but physically responsive to estrogen replacement. A 46XX karyotype is not associated with gonadal neoplasia.

The 46 XO karyotype is found in patients with Turner's syndrome. It is a frequent malformation found in approximately 1 out of every 2,500 live female births. The physical findings of bilateral streak gonads, short stature, webbed neck, facial dysmorphism, and sexual infantilism are due to the total or partial loss of the chromosomal information from one of the two X chromosomes. Renal anomalies are common with horseshoe kidney being the most common. Cardiovascular anomalies found with this syndrome include bicuspid mitral valve and aortic coarctation. Management is directed at correcting physical anomalies. Short stature may respond to human growth hormone. Most will require hormone replacement therapy at puberty to develop secondary sexual characteristics. Fertility is
rare but reported.

Patients with pure gonadal dysgenesis and a 46XY karyotype will display variable degrees of undermasculinization dependent upon the amount of testicular dysplasia. Because testicular secretion of MIS may also be deficient, retained müllerian ductal structures are also common. Patients with 46XY karyotype are at an increased risk of gonadoblastoma occurrence. As a general rule, patients found early are reared as females with gonadectomy, clitoral reduction, vaginoplasty, and estrogen/progesterone replacement starting at puberty. In patients who present late and are committed to male gender assignment, they can undergo hypospadias repair, removal of müllerian duct structures, and gonadectomy. They should receive androgen therapy starting at puberty.

**Mixed gonadal dysgenesis.** Patients with mixed gonadal dysgenesis have been categorized as having “partial gonadal dysgenesis” secondary to Y chromosome mosaicism (Kim et al., 2002). The majority of patients will have a 45 XO/46XY karyotype, and it is characterized by a unilateral testis, a contralateral streak gonad, persistent müllerian duct structures ipsilateral with the streak gonad, and varying levels of external genitalia undervirilization (Diamond, 2002). In the newborn period, mixed gonadal dysgenesis is the second most common cause of ambiguous genitalia, after congenital adrenal hyperplasia. There is an estimated incidence of gonadal tumor (gonadoblastoma or dysgerminoma) of approximately 15% to 20%. Most commonly, this occurs in the dysgenetic testis. These patients also have an increased incidence of Wilms’ tumor and Denys-Drash syndrome characterized by progressive nephropathy (Diamond, 2002). The management of patients with mixed gonadal dysgenesis consists of Wilms’ tumor screening, gender assignment, appropriate gonadectomy, and genital reconstruction. Two-thirds of patients are reared as females. If the patient is highly masculinized and the decision is made to rear the child as a male with testis preservation, careful periodic screening of the testis must be undertaken due to the risk of malignancy.

**True hermaphrodites.** The phenotype associated with true hermaphrodites varies between the extremes of female/male differentiation. However, the majority of patients show some signs of virilization. There are regional differences in the incidence, time of diagnosis, and karyotype of true hermaphrodites. While it is rare in the West, it is one of the more common types of intersex in Africa (Kuhnle, Krob, & Maier, 2003). Most children are found at birth because of this partial virilization; however, in the Third World, late presentation is common. Regional variation in karyotype show that in Africa, 46XX is most common, in Europe and North America, mosaicism is more common (46XX/46XY and 47XXX/46XY), and in Japan, 46XY is common.

The hallmark of true hermaphroditism is the finding of gonads with both testicular and ovarian tissue; the latter being different from a streak by the presence of a well-formed follicle. Ovarian tissue generally matures normally with follicular maturation at puberty. Testicular tissue by contrast, will often have progressive fibrosis with age and spermatogenesis is rare. Hormonal production usually follows histologic changes. At birth, the ability to produce testosterone may be normal, but it becomes progressively impaired later in adolescence as testicular fibrosis becomes more evident. Internal ducts follow ipsilateral gonadal histology. Tumors may arise, most commonly gonadoblastoma and dysgerminoma; however, in patients diagnosed and managed early, malignant degeneration is rare.

The diagnosis of true hermaphroditism is via chromosomal analysis, imaging, and hormonal studies which usually precede open or laparoscopic exploration. Imaging with sonography may reveal uterine and ovarian structures. Genitogram may outline a vagina, cervix, uterine cavity, and fallopian tubes. Endocrine studies include a HCG stimulation test in which a rise in serum testosterone following HCG administration is indicative of functioning testicular tissue. Histologic confirmation of the condition rests with gonadal biopsy. Management consists of removing the conflicting gonadal tissue, genital reconstruction that best agrees with the sex of rearing, and potential hormonal supplementation at puberty.

**Modern Controversy**

Medical science has advanced to where we have a greater understanding of the biochemical pathways that lead to intersex and we often have the surgical expertise to physically produce either male or female gender based on the parents’ and physicians’ best judgments. What must be stressed is that the gender we chose for the infant may not be the gender he or she chooses for him or herself. Science is still ignorant of many of the psychological factors that determine gender identity. Some studies have indicated a psychosexual development that is congruent with gender, such as female psychosexual identity in female pseudohermaphrodites with congenital adrenal hyperplasia (Hines, 2004). Other studies have pointed out that many factors are involved in sexual identity beyond chromosomal makeup (Diamond, 2004). Many of these factors may involve early imprinting of the brain based on
hormonal exposure. This, taken in consideration with changes in societal acceptance and expectations, have led many physicians, parents, and patients to delay surgical reconstruction until the patient is of an age to be part of the decision process.

The Internet is a fantastic tool for distributing information. However, often it is unfiltered information, which may be emotionally biased. A Internet search using the Google search engine revealed 94,700 different hits for the term “intersex,” with the top three sites being the Intersex Society of North America, the United Kingdom Intersex Society, and the Intersex Support Group International. The opening statement on the Intersex Society of North America’s Web site is, “The Intersex Society of North America (ISNA) is devoted to systemic change to end shame, secrecy, and unwanted genital surgeries for people born with an anatomy that someone decided is not standard for male or female.” Popular media and trial lawyers have latched onto the controversies of intersex surgery. Both the television program 60 Minutes and the magazine Newsweek have presented stories of patients as adults with gender dissatisfaction. Gender assignment is a tough decision and some now advocate that no decision be made. Anyone who chooses to deal with these patients must realize that many factors go into the decision to perform surgery. The ideal outcome, a patient with a healthy self-esteem and a satisfied gender assignment, cannot be known in the infant period. Some would argue that the patients themselves should decide when they reach an age of appropriate understanding. However, this ignores the reality of societal pressures that segregate expectations, social structures, and peer pressure along gender lines. Clearly it is not an easy decision, but one in which pediatric urologists, pediatricians, and potentially mental health professionals attempt to provide guidance to the parents towards the child’s well-being.

Case Studies

Case 1 is an 18-month-old female brought in by the parents with the complaint of new onset of pubic hair. She was the product of a normal, term pregnancy with no remarkable prenatal events. With the exception of the pubic hair, she is without physical complaints and has a negative past medical history. The family mentioned that a cousin had died in infancy of unknown causes. Her physical finding is seen in Figures 3a-d. Remarkable findings include pubic hair, an enlarged, prominent clitoris, and fusion of the labia minora along the midline. There were no palpable gonads, and cystoscopy reveals a normal appearing cervix. Pelvic ultrasound shows a normal-appearing uterus and ovaries. Renal ultrasound is remarkable for bilaterally enlarged adrenal glands. Her serum electrolytes are within normal limits. Urinary and serum 17-hydroxyprogesterone are markedly elevated. The patient is diagnosed with 21-hydroxylase deficiency and congenital adrenal hyperplasia without salt wasting. She is started on cortisol replacement and undergoes feminizing genitoplasty.
Case 2. Figures 4a-b shows a newborn infant with a 3 cm perineal level hypospadiac phallus and bilaterally nonpalpable gonads but a right inguinal hernia. Examination shows what appears to be a right inguinal hernia. Serum cortisol and precursor levels are all within normal limits. Karyotype shows 46XY, but is SRY antigen negative.

Pelvic sonography appears to show bilateral gonads at the level of the internal inguinal ring. There appears to be a vagina and uterus on sonography. Figure 5 shows the results of the genitogram. The perineal opening is catheterized and contrast injected. A common urogenital channel is seen with bifurcation into an urethral/bladder channel and what appears to be a vagina. This finding is confirmed on cystoscopy, which shows a common channel branching into a normal urethra, bladder neck, and bladder. The second channel is a vagina with a normal appearing cervix. Initial serum testosterone levels are low but there is a marked elevation of testosterone levels in response to human chorionic gonadotropin, indicating active testicular tissue.

Figure 6 shows the results of pelvic exploration. On the right side, gonadal biopsy shows testicular tissue fused with dysplastic ovarian tissue (ovotestis). On the left, ovarian tissue appropriate for age is encountered. The diagnosis of true hermaphrodite is made with the decision to pursue a female gender assignment based on future fertility potential, endocrine considerations, as well as genital functionality. She undergoes removal of the right ovotestis, clitoral recession, and vaginoplasty.

Conclusion

Science has revealed many of the genetic and hormonal pathways responsible for intersex disorders and today we possess the surgical skill to give most patients the appearance of either male or female gender, according to our wishes. The underlying chromosomal anomalies and surgical intervention were discussed; yet, we have only begun to study the psychological aspects of sexuality and the developing fetal brain. The psychological aspects of the physical statement of gender assignment could perhaps be
even more critical in the final picture of social adjustment. In dealing with intersex, the clinician has the responsibility of educating the parents about both the medical science we understand, as well as the physical/psychological aspects of sexuality which are still poorly understood.

References


