Chapter 43. Disorders of Sex Development

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Disorders of Sex Development: Introduction

What defines our sexuality is a complex interaction between our genetic makeup, environmental stimulus, and cultural influences. The origins of our sexuality occur at the time of conception when the genetic material from two sources of the opposite sex coalesces into a new individual. From that moment, sexual differentiation occurs by a highly organized process. Sex chromosomes and autosomes dictate the development of gonads; the gonads in turn produce hormones, which then direct the development of the internal and external genitalia. Disorders of sex development (DSD) or differentiation arise from abnormalities in chromosomes, gonadal development, or hormonal production/activity.

Patients with DSD become apparent (1) during the newborn period as having ambiguous genitalia or a discordant phenotypic from the genotype found at the time of amniocentesis, (2) as having inappropriate pubertal development, (3) as having delayed pubertal development, or (4) later in life as having infertility.

Normal Sexual Differentiation

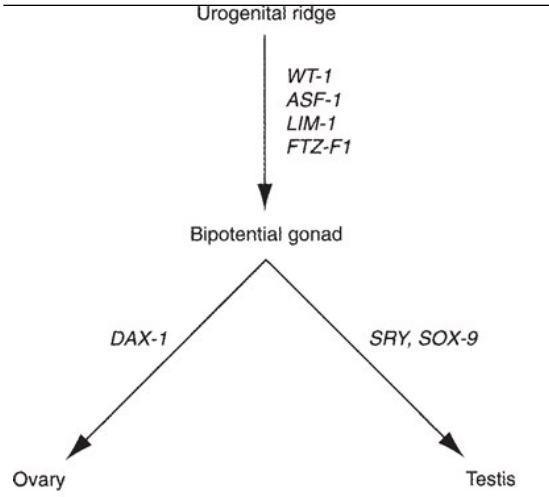
Chromosomal Sex

The genetic material necessary for the development of the male phenotype is normally located on the short arm of the Y chromosome (Wilson et al, 1981). The critical gene or sex-determining region on the Y chromosome is known as the SRY region. The gene products of the SRY genetic cascade direct the development of the testis by interacting with multiple other genes such as *SOX-9* (Conte and Grumbach, 2007). Genetic information that is known to be necessary for male and female development beyond gonadal differentiation is located on the X chromosome and on the autosomes.

Gonadal Differentiation

The gonads develop from the urogenital ridges (Figure 43–1), which are formed during the 4th week of gestation by the proliferation of the coelomic epithelium and condensation of the underlying mesenchyme along the mesonephros. The germ cells, located in the endoderm of the yolk sac, migrate to the genital ridges. At the early stage of development, the gonad is bipotential, capable of forming into either a testis or an ovary. During the 6th–7th week of gestation, at least four different genes, Wilms' tumor suppressor gene (*WT-1*), Fushi-Tarza Factor-1 (*FTZ-F1*), steroidogenic Factor-1 (*SF-1*), and *LIM-1*, induce the development of the testis. The primordial germ cells differentiate into the Sertoli cells and associated Leydig cells, which aggregate into spermatogenic cords. Loose mesenchymal tissue condenses into a thick layer, the tunica albuginea, which surrounds the testis and separates its connection with the coelomic epithelium, thereby preventing further migration of mesonephric cells into the testis.

Figure 43–1.



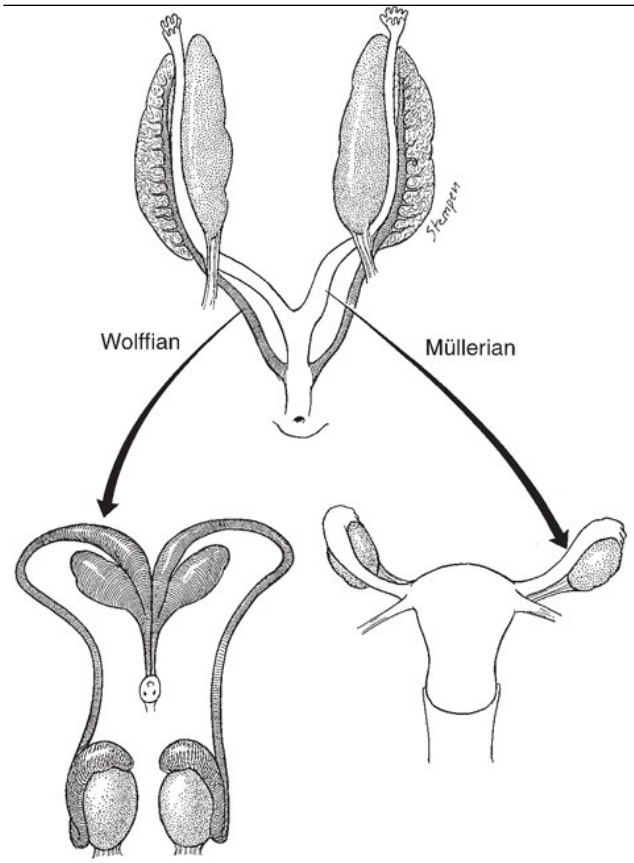
Sex-determining genes involved in testes and ovarian development.

Classic teaching is that the female phenotype is the default developmental pathway in the absence of the SRY cascade. It is now known that at least one gene, dosage-sensitive sex reversal (*DAX-1*), is essential for ovarian development. *DAX-1* is located on the short arm of the X chromosome. The gene products of *SRY* and *DAX-1* compete to stimulate the steroidogenic acute regulatory protein (StAR). The StAR protein is the first step in steroidogenesis, facilitating the conversion of cholesterol to pregnenolone. In the normal XY male, *SRY* overwhelms the one functional *DAX-1* gene, stimulating testicular development and subsequent testosterone production. In the normal XX female, two *DAX-1* genes are present without the competitive *SRY*, downregulating StAR, hence inhibiting testicular development, which results in ovarian development. In the fetal ovaries, the germ cells differentiate and are arrested in the last phase of meiotic prophase, forming the oocytes. The cells in the genital ridges develop into granulosa cells, which surround the oocytes and complete the formation of the ovaries.

Hormones

At 3.5 weeks' gestation, the Wolffian system appears as two longitudinal ducts connecting cranially to the mesonephros and caudally draining into the urogenital sinus (Figure 43–2). At approximately the 6th week of gestation, the Müllerian duct develops as an evagination in the coelomic epithelium just lateral to the Wolffian duct.

Figure 43–2.



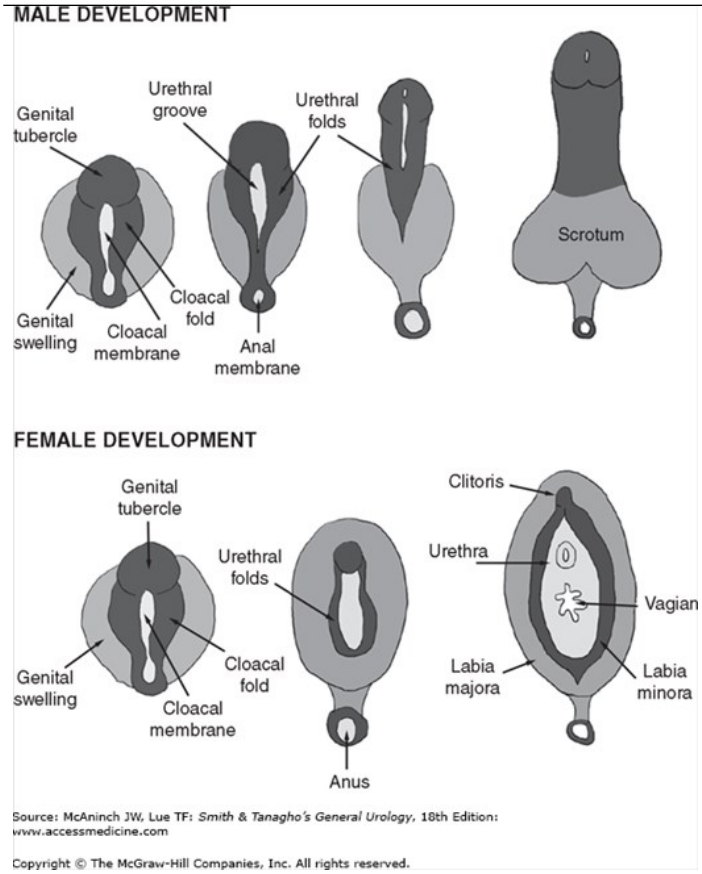
Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Schematic of male (Wolffian) and female (Müllerian) internal and external genital development from common origin.

During the 8th–9th week of gestation, Sertoli cells of the fetal testis secrete a glycoprotein, Müllerian-inhibiting substance (MIS), or anti-Müllerian hormone. This protein induces the regression of the Müllerian ducts through the dissolution of the basement membrane and condensation of mesenchymal cells around the Müllerian duct. Because MIS acts locally, Müllerian duct regression occurs only on the ipsilateral side of the fetal testis producing this hormone. MIS also induces the formation of seminiferous tubules and further differentiation of the testis. At the 9th or 10th week of gestation, the Leydig cells appear in the testis and begin to synthesize testosterone. This hormone transforms the Wolffian duct into the male genital tract, which is completed by the end of the 11th week of gestation.

Beginning in the 9th week of gestation, testosterone also induces the development of the external genitalia (Figure 43–3) from the genital tubercle, urogenital sinus, and genital swellings (Jirasek et al, 1968). At the molecular level, testosterone is converted to 5α-dihydrotestosterone (DHT) by the microsomal enzyme, type 2 5α-reductase, for complete differentiation of the penis with a male-type urethra and glans (Wilson et al, 1993). Testosterone dissociates from its carrier proteins in the plasma and enters cells via passive diffusion. Once in the cell, testosterone binds to the androgen receptor (AR) and induces changes in conformation, protecting it from degradation by proteolytic enzymes. This conformational change is also required for AR dimerization, DNA binding, and transcriptional activation, all necessary for testosterone to be expressed. Androgen binding also displaces heat shock proteins, possibly relieving constraints on receptor dimerization or DNA binding. After entering the nucleus, the AR complex then binds androgen response element DNA regulatory sequences within the androgen responsive genes and activates them. DHT also binds the AR, with enhanced androgenic activity, in part because of its slow dissociation rate from the AR.

Figure 43–3.



Differentiation of the male and female external genitalia from the indifferent stage to full differentiation (8–16 weeks). (Illustrations by Dr Hiep Nguyen.)

DHT then binds to nuclear receptors, forming a complex that regulates the transformation of these tissues into the glans penis, penile and cavernous urethra, Cowper's glands, prostate, and scrotum. Between the 28th and 37th week of gestation, testicular descent into the scrotum begins. While the mechanism of this process is not completely understood, it is clearly androgen dependent.

Development of the Female Genitalia

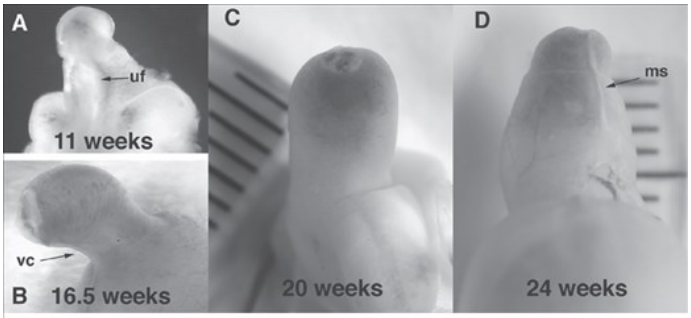
The female internal genitalia develop from the Müllerian ducts. Without the hormones produced by the testis, the Wolffian ducts regress at the 9th week of gestation. At the same time, the Müllerian ducts begin to differentiate; the cranial portions form the fallopian tubes, while the caudal portions fuse to form the uterus, cervix, and the upper portion of the vagina. Concurrently, the external genitalia defined as the lower portion of the vagina, the vestibule, Bartholin and Skene glands, the clitoris, and labia minora and majora develop from the urogenital sinus and genital tubercles. Like the testis, the ovary undergoes a partial transabdominal descent. However, transinguinal descent of the ovary does not occur, leaving the ovaries just below the rim of the true pelvis. The role of estrogen in the differentiation of the female phenotype is unclear.

Development of the Male External Genitalia

Formation of the external male genitalia is a complex developmental process involving the SRY genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. By the end of the 1st month of gestation, the hindgut and future urogenital system reach the ventral surface of the embryo at the cloacal membrane. The urorectal septum divides the cloacal membrane into a posterior, or anal, half and an anterior half, the urogenital membrane. Three protuberances appear around the latter. The most cephalad is the genital tubercle. The other two, the genital swellings, flank the urogenital membrane on each side. Up to this point, the male and female genitalia are essentially indistinguishable. Under the influence of testosterone in response to a surge of luteinizing hormone from the pituitary, masculinization of the external genitalia takes place. One of the first signs of masculinization is an increase in the distance between the anus and the genital structures, followed by elongation of the phallus, formation of the penile urethra from the urethral groove, and development of the prepuce.

At 8 weeks' gestation, the external genitalia remain in the indifferent stage. The urethral groove on the ventral surface of the phallus is between the paired urethral folds. The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds. As development progresses, the ectodermal edges of the urethral groove begin to fuse to form the median raphe (Figure 43–4A). By 11–12 weeks, the coronal sulcus separates the glans from the shaft of the penis. By 16 weeks' gestation, the urethral folds have completely fused in the midline on the ventrum of the penile shaft (Figure 43–4B). Note the normal ventral penile curvature, or chordee, that occurs during development and resolves by the 20th week (Figure 43–4C).

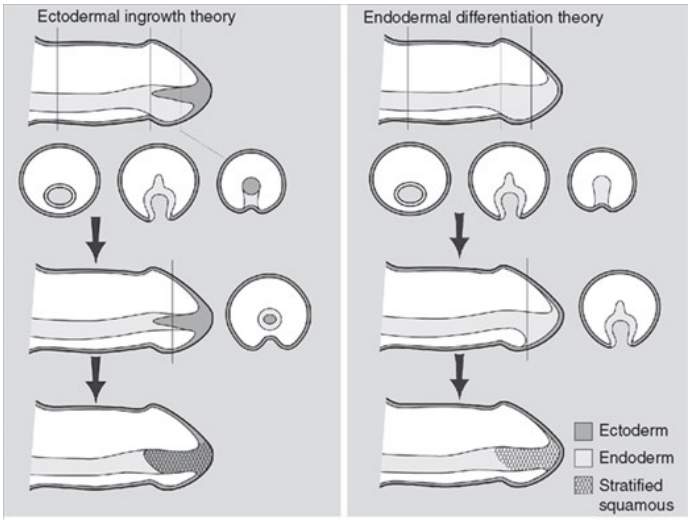
Figure 43–4.



Male human fetal external genitalia during gestation. ***A:*** 11 weeks. Note the urethra is open and urethral fold (uf) and groove are prominent in the transillumination view of the phallus. ***B:*** 16.5 weeks. Note the normal ventral curvature (vc) as well as the foreskin, which is almost completely formed. ***C:*** At 20 weeks' gestation, penile and urethral development looks complete, with the prepuce covering the glans and the penile curvature resolving. ***D:*** At 24 weeks, the prepuce covers the whole glans. Note the midline seam (ms). Note the progression of natural curvature to a straight phallus during development.

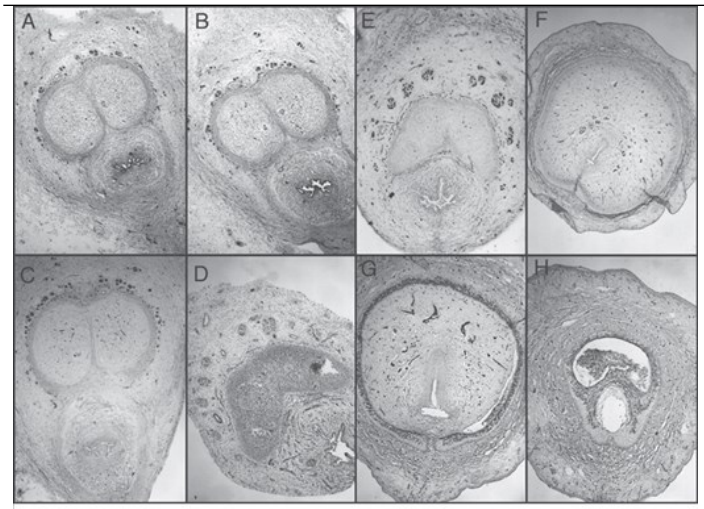
The glandular urethra, which consists of a squamous epithelial-lined tube different from the urothelial-lined anterior urethra, also completes its formation during this period. The mechanism of the glandular urethral formation remains controversial. Evidence suggests two possible explanations (Figure 43–5): (1) endodermal cellular differentiation where the glandular urethra forms by an extension of urogenital sinus epithelium that undergoes transdifferentiation versus (Kurzrock et al, 1999) (2) primary intrusion of the ectodermal tissue from the skin of the glans penis. Cross-sectional histologic analysis at 24 weeks' gestation reveals complete penile development (Figures 43–6A–H). Note the extensive neuronal innervation just above the tunica of the corporeal bodies. Three-dimensional reconstruction of the fetal male penis illustrates the extensive neuronal distribution (Figure 43–7). Note the nerve density in the glans (Figures 43–7E and F).

Figure 43–5.



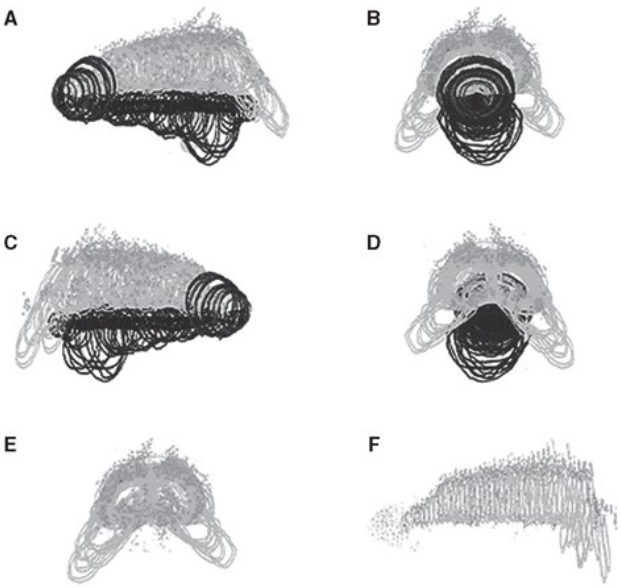
Theories of human penile urethral development. The ectodermal ingrowth theory as described in most textbooks of embryology postulates that the glanular urethra is formed by ingrowth of epidermis. More recent data support the formation of the entire urethra via endodermal differentiation alone.

Figure 43–6.



Normal human fetal penis, 24 weeks (***A–H***). Transverse histologic sections show immunohistochemical localization with the neuronal marker S-100 (25×). Note localization of S-100 nerve marker (dark staining) completely surrounding the cavernous bodies up to the junction with the urethral spongiosum along the penile shaft except at the 12 o'clock position (***A–D***). On the proximal penis at the point where the corporeal bodies split into two (***E***) and continue in a lateral fashion inferior and adjacent to the pubic rami, the nerves localize to an imaginary triangular area at the 11 o'clock and 1 o'clock positions. At this point (***E***), the nerves reach their furthest vertical distance from the corporeal body (approximately one-half the diameter of the corporeal body) and continue (***F–G***) in a tighter formation at the 11 o'clock and 1 o'clock positions well away from the urethra.

Figure 43–7.



Normal human fetal penis, 45 weeks' gestation. Four views of a computer-generated three-dimensional reconstruction (***A***, side; ***B***, front; ***C***, side; ***D***, back, ***E***, front [without urethra]; ***F***, side [without urethra]). Note the nerves along the outside of the tunica of the corporeal bodies and their absence at the 12 o'clock position. Note the impressive glandular innervation in ***E*** and ***F***.

Anatomical and immunohistochemical studies advocate the new theory of endodermal differentiation, which shows that epithelium of the entire urethra is of urogenital sinus origin. The entire male urethra, including the glandular urethra, is formed by dorsal growth of the urethral plate into the genital tubercle and ventral growth and fusion of the urethral folds. Under proper mesenchymal induction, urothelium has the ability to differentiate into a stratified squamous phenotype with characteristic keratin staining, thereby explaining the cell type of the glans penis.

The future prepuce is forming at the same time as the urethra and is dependent on normal urethral development. At about 8 weeks' gestation, low preputial folds appear on both sides of the penile shaft, which join dorsally to form a flat ridge at the proximal edge of the corona. The ridge does not entirely encircle the glans because it is blocked on the ventrum by incomplete development of the glandular urethra. Thus, the preputial fold is transported distally by active growth of the mesenchyme between it and the glandular lamella. The process continues until the preputial fold (foreskin), covers all of the glans, forming a midline seam (Figure 43–4D). The fusion is usually present at birth, but subsequent desquamation of the epithelial fusion allows the prepuce to retract. If the genital folds fail to fuse, the preputial tissues do not form ventrally; consequently, in hypospadias, preputial tissue is absent on the ventrum, and excessive dorsally.

Disorders of Sexual Differentiation

Disorders of abnormal sexual differentiation may be divided into the following three categories.

Disorders of Chromosomal Sex

These result from abnormalities in the number or structure of the sex chromosomes. These abnormalities may arise from nondisjunction, deletion, breakage, rearrangement, or translocation of genetic material on these chromosomes. These disorders are summarized in Table 43–1.

Table 43–1. Disorders of Chromosomal Sex.

Disorder	Pathology	Chromosomes	Incidence	Gonads	Internal genitalia	External genitalia	Other features	Risk of cancer	Treatment
47,XXY (Klinefelter syndrome)	Extra X chromosome	47,XXY 46,XY/47,XXY	1 in 500	Hyalinized testis No spermatogenesis	Wolffian	Male	Gynecomastia Tall stature Mild mental retardation Elevated FSH/LH Low testosterone Elevated estradiol Infertility	Breast Extragonadal germ cell	Supplemental androgens Surgery for severe gynecomastia
XX male (XX sex reversal)	No Y chromosome Usually TDF (+)	46,XX	1 in 20,000–24,000	Hyalinized testis No spermatogenesis	Wolffian	Male	Gynecomastia Short stature Inc. incidence of hypospadias Normal mental status May be familial	Rare germ cell	Same as Klinefelter
45,X (Turner's syndrome)	Absence of X chromosome	45,X 46,XX/45,X Some contain Y chrom. elements	1 in 2700	Streak gonads No germ cells	Müllerian	Immature female	Short stature Little breast development Web neck and other somatic abn. Cardiovascular abn. (ie, coarctation) Renal abn. (Horseshoe or malrotation) Autoimmune dz. (hypothyroid,	Germ cell Y-chrom mosaic	Supplemental estrogen Removal of streak gonads in Y-chrom. mosaic

							diabetes) Infertility Amenorrhea		
45,X/46,XY DSD (Mixed gonadal dysgenesis)	Incompl. virilization & Müllerian regression	45,X/46,XY (70%) Undetected mosaic		One testis (usually undescended) and streak gonad	Wolffian and Müllerian	Usually ambiguous 60% reared as female	Somatic features like 45,X	Germ cell	Female —Prophylactic gonadectomy Male —Streak gonads removed —Intra-abd. testis excised unless can be relocated and no ipsilateral Müllerian structure present
Ovotesticular DSD (True hermaphrodite)	Unknown	46,XX (70%) 46,XY (10%) Mosaic	Unknown	Bilateral ovotestis Ovotestis & ovary or testis (40%) One ovary & testis (40%)	Wolffian and Müllerian	Usually ambiguous 70% reared as male	Gynecomastia at puberty Menstruation at puberty May be familial	Rare germ cell	Reconstructive surgery Poss. remove gonads

Disorders of Gonadal Sex

These result from abnormalities in gonadal development. In these disorders, the karyotype is normal (ie, 46,XX or 46,XY). However, mutations in the sex chromosomes or autosomes, teratogens, or trauma to the gonads interfere with their normal development. These disorders are summarized in Table 43–2.

Table 43–2. Disorders of Gonadal Sex.

Disorder	Pathology	Chromosomes	Incidence	Gonads	Internal genitalia	External genitalia	Other features	Risk of cancer	Treatment
Complete gonadal dysgenesis (Swyer Syndrome)	Unknown mutation prevents nl. differentiation of gonads	46,XX 46,XY	1 in 8000	Bilateral streak gonads	Müllerian	Immature female	Normal to tall stature Minimal somatic abn. Female: estrogen def. Male: testosterone def. May be familial	Germ cell in 46,XY	Estrogen supplement Remove gonads in 46,XY
Absent testes syndrome	Mutation, teratogen or trauma to testis	46,XY	Unknown	Absent/rudiment testis No streak gonads	Wolffian	Var. virilization	Normal	Usually none	Female —Estrogen supplement —Reconstructive surgery Male —Androgen supplement

Disorders of Phenotypic Sex

These result from abnormalities in hormonal production or activity. The etiologies include defective synthesis by the gonads, abnormal production by the adrenal glands, the presence of exogenous sources, or abnormalities in receptor activity. These disorders are summarized in Table 43–3.

Table 43–3. Disorders of Phenotypic Sex.

Disorder	Pathology	Chromosomes	Incidence	Gonads	Internal genitalia	External genitalia	Other features	Urinary steroids	Risk of cancer	Treatment
46,XX DSD (Female Pseudohermaphrodite)										
3 β-Hydroxysteroid dehydrogenase def.	Excess androgens	46,XX	Second most common of CAH	Ovary	Müllerian	Mild ambiguous	Severe salt wasting No cortisol No aldosterone	DEAS	None	Replacement mineralocorticoids and glucocorticoids Reconstruction as needed
11 β-Hydroxy lase def.	Excess androgens	46,XX	Rare	Ovary	Müllerian	Ambiguous	Hypertension Dec. cortisol Dec. aldosterone	11 DCS 11 DOC	None	Replacement glucocorticoids
21 α-	Excess	46,XX	1 in 5000–	Ovary	Müllerian	Ambiguous	Normal	17 OH-P	None	Reconstruction as

Hydroxylase def.—Partial	androgens		15,000				cortisol Inc. aldosterone			needed
—Severe	Excess androgens	46,XX		Ovary	Müllerian	Ambiguous	Severe salt wasting Dec. cortisol Dec. aldosterone	17 OH-P	None	Replacement mineralocorticoids and glucocorticoids Reconstruction as needed
Excess maternal androgens	Excess androgens	46,XX		Ovary	Müllerian	Ambiguous	Drugs such as progestational agents Virilizing ovarian Adrenal tumors	None	None	None
46,XY DSD (Male Pseudohermaphrodite)										
20,22 Desmolase def.	Defect in testosterone synthesis	46,XY		Testis	Wolffian	Ambiguous	Severe salt wasting No cortisol No aldosterone	None	None	Replacement mineralocorticoids and glucocorticoids
3 β-Hydroxy steroid dehydrogenase def.	Defect in testosterone synthesis	46,XY	Second most common in CAH	Testis	Wolffian	Ambiguous	Severe salt wasting No cortisol No aldosterone	DEAS	None	Replacement mineralocorticoids and glucocorticoids Reconstruction as needed
17 α-Hydroxylase def.	Defect in testosterone synthesis	46,XY		Testis	Wolffian	Ambiguous	Hypokalemic alkalosis Hypertension Dec. cortisol Dec. aldosterone Gynecomastia	CS 11 DCS	None	Replacement glucocorticoids
17,20 Desmolase def.	Defect in testosterone synthesis	46,XY	Rare	Testis	Wolffian	Ambiguous	Normal cortisol and aldosterone		None	Supplemental testosterone
17 β-Hydroxysteroid dehydrogenase def.	Defect in testosterone synthesis	46,XY	Most common	Testis	Wolffian	Ambiguous	Virilization and puberty	ASD	None	Decision reared as female or male
5 α-Reductase def.	Defect in androgen action	46,XY —Autosomal rec.		Testis with spermatogenesis	Wolffian	Female	No gynecomastia Nl. testosterone Nl. virilization	None	None	None

Complete androgen Insensitivity syndrome	Androgen receptor defect	46,XY —X linked	1 in 20,000–64,000	Testis not fertile	Absent	Female reared as female	Inc. testosterone Inc. estrogen	None	Germ cells	Remove gonads after puberty Estrogen replacement
Partial androgen Insensitivity syndrome	Androgen receptor defect	46,XY —X linked rec.	1/10th of complete	Testis not fertile	Wolffian	Female Versus severe hypospadias	Inc. testosterone Inc. estrogen	None	Germ cells	Depends on sex of rearing
Infertile male syndrome	Androgen receptor defect	46,XY —? X linked rec.		Testis not fertile	Wolffian	Male	Infertility Nl. or inc. testosterone Nl. or inc. estrogen	None	None	None
Persistent Müllerian duct syndrome	Persistent Müllerian ducts	Unknown		Testis	Wolffian with rudimentary uterus and tubes	Male usually cryptorchid	Nl. testosterone Nl. estrogen	None	None	Orchiopexy Leave uterus and tubes

Clinical Evaluation of Patients with Ambiguous Genitalia

The accurate diagnosis of a patient with ambiguous genitalia is a challenging process. Based on the diagnosis, decisions will be made for gender assignment, which will have a great impact not only on the patient but also on the patient's family (Daaboul and Frader, 2001; Morland, 2001; Conte and Grumbach, 2007). In most societies, the accepted norm is two sexes, either male or female. When a new baby arrives and the proclamation as to whether it is a boy or a girl cannot be made immediately, an anticipated celebration turns into a stressful family dilemma. With prenatal amniocentesis and routine ultrasound, sex determination is often known well before birth. This can compound the emotional trauma when the known and anticipated genotype does not match the newborn's phenotype. Furthermore, in cases such as severe salt-wasting congenital adrenal hyperplasia (CAH), accurate diagnosis is lifesaving.

History

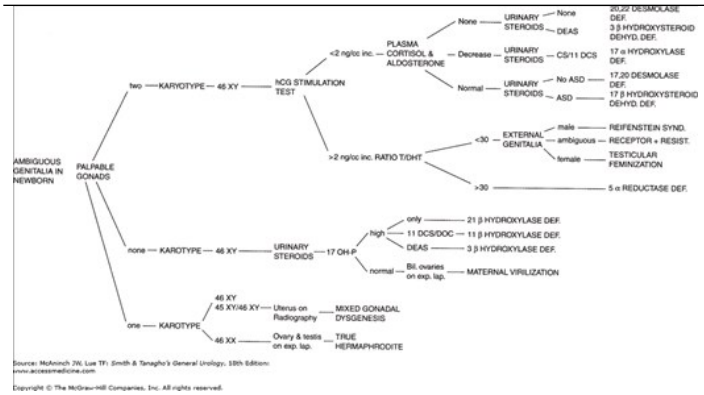
A detailed history is of great importance. Since many of the disorders such as XX male syndrome and true hermaphrodites are hereditary, a family history should carefully be examined for similarly affected individuals, unexplained death during infancy, infertility, amenorrhea, and hirsutism. Furthermore, drugs ingested during pregnancy (such as progesterone) and virilizing signs in the mother during pregnancy should be ascertained.

Physical Examination

The abdomen and rectum should be carefully palpated for midline structures such as a uterus. These examinations will provide information regarding the presence of Müllerian duct derivatives. Other helpful physical findings include dehydration, failure to thrive, pigmentation (in patients with salt-wasting CAH), and the presence of other associated anomalies such as cardiac murmurs or web neck (in patients with Turner's or Klinefelter syndrome).

It is important to palpate for gonads in the labioscrotal fold or the scrotum. Since ovaries do not descend, it is likely to be a testis and hence unlikely to represent a case of 46,XX DSD (female pseudohermaphroditism). Based on the presence or absence of gonads, an algorithm can be followed to determine the differential diagnosis of patients with ambiguous genitalia (Figure 43–8). It is important to look at the size of phallus (Table 43–4) and the location of the urethral meatus (Camurdan et al, 2007). Any patients with bilateral cryptorchidism or with unilateral cryptorchidism with hypospadias should be suspected of having abnormalities in sexual differentiation. As noted, other helpful physical findings include hyperpigmentation of the areola and labioscrotal fold, common in patients with CAH.

Figure 43–8.



Clinical approach to intersex. Algorithm based on palpating gonads. Bil., bilateral; CS/11 DCS, corticosterone/deoxycortisol; DEAS, 1,3-bis[4-(diethylamino)-2-hydroxy phenyl]-2,4-dihydroxycyclobutenediylium dihydroxide, bis(inner salt); DCS/DOC, deoxycortisol costerone; def., deficiency; dehyd., dehydration; 17 OH-P, 17 hydroxy progesterone; exp. lap., exploratory laparoscopy; resist., resistance; synd., syndrome; T/DHT, testosterone/dihydrotestosterone.

Table 43–4. Normal Values for Stretched Penile Length.

Age	Length (cm) (Mean ± SD)
Premature 30 wk	2.5 ± 0.4
Full-term newborn	3.5 ± 0.4
0–5 months	3.9 ± 0.8
6–12 months	4.3 ± 0.8
1–2 y	4.7 ± 0.8
2–3 y	5.1 ± 0.9
3–4 y	5.5 ± 0.9
5–6 y	6.0 ± 0.9
10–11 y	6.4 ± 1.1
Adult	12.4 ± 2.7

Chromosomal Evaluation

Examination of buccal mucosal cells for Barr body (inactivated second X chromosome) cannot be relied on to make an accurate diagnosis in patients with ambiguous genitalia.

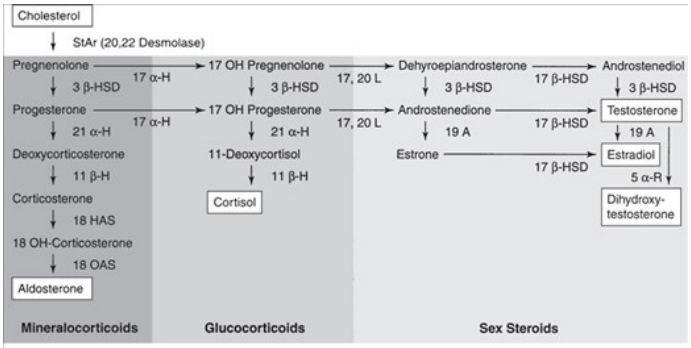
A more accurate but more time-consuming method (2–3 days) is the direct assessment of chromosomes from cultured peripheral blood leukocytes. This method provides the exact chromosomal complements, the presence of mosaicism, and structural features of the chromosomes.

In the case of mosaicism, several different tissue samples may be required to accurately confirm the genotype.

Biochemical Evaluation

In the case of CAH, the specific enzyme defect can be determined based on the presence or absence and the type of steroid excreted in the urine. Figure 43–9 depicts the steroid synthesis pathway from cholesterol to aldosterone, steroids, or DHT. Note the enzymes necessary for conversion from precursors to products (also see Table 43–3).

Figure 43–9.



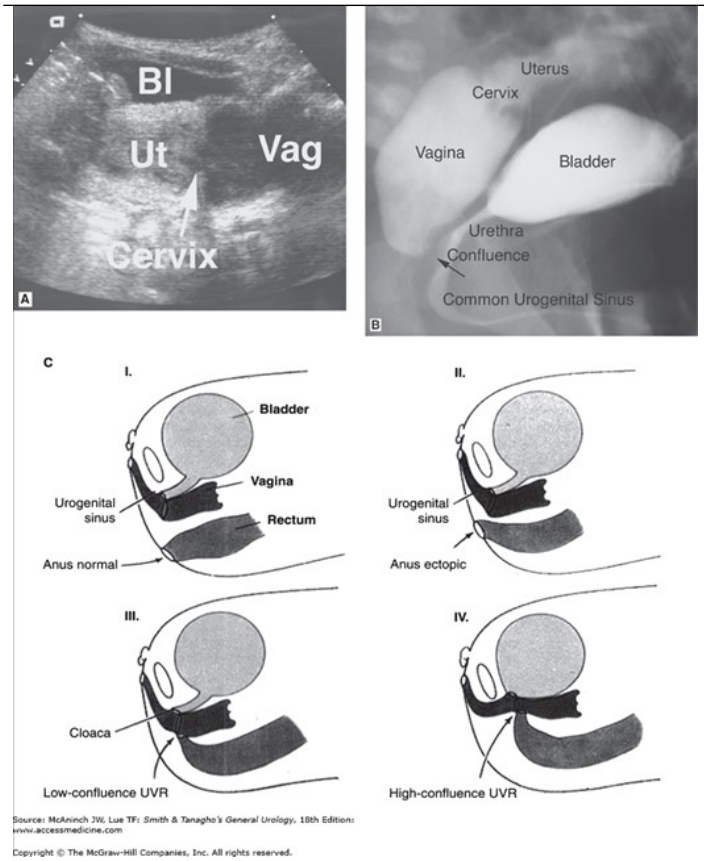
Pathway of steroid hormone biosynthesis and possible enzyme deficiencies. 3β-HSD, 3β-hydroxysteroid dehydrogenase; 21α-H, 21α-hydroxylase; 11β-H, 11β hydroxylase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 18 HAS, 18 hydroxy-aldosterone synthetase; 18 OAS, 18 oxidase-aldosterone synthetase; 5α-R, 5α reductase; 19A, 19 aromatase; StAR, steroidogenic acute regulatory protein.

In other disorders caused by hormonal abnormalities (such as 5α-reductase deficiency and androgen resistance), direct measurement of plasma testosterone is often not helpful, since abnormalities in testosterone levels in these pathologic states have not been consistently characterized. A more useful test is the testosterone response following stimulation by human chorionic gonadotropin (hCG) (2000 IU/day for 4 days). If plasma testosterone levels rise >2 ng/mL from baseline, the abnormality is consistent with androgen resistance rather than a defect in testosterone synthesis. In addition, this test is also used to diagnose 5α-reductase type 2 deficiency. A post-hCG stimulation ratio of testosterone to DHT >30 establishes this diagnosis.

Radiographic Evaluation

In patients with intersex disorders, ultrasonography provides the least invasive and safest means of imaging the abdomen and pelvis. Identification of Müllerian-derived structures such as the uterus and fallopian tubes will be important in determining the diagnosis (Figure 43–10A). The adrenal glands can also be examined for enlargement. While this finding is not diagnostic for CAH, it is suggestive and can direct further evaluation. Magnetic resonance imaging can provide a more detailed examination of the abdomen for internal genital structures. However, in most cases, anesthesia is needed for a good-quality magnetic resonance imaging examination. Injecting radiographic contrast material through the opening in the urogenital sinus is helpful in delineating the internal duct structures. It is most useful in assessing the presence of vagina, cervix, fallopian tube, utricle, and the connection with the urethra (Figures 43–10B and C). Genitography will also provide needed anatomical information for future reconstructive surgery.

Figure 43–10.



A: Newborn sonogram revealing a uterus (Ut) behind the bladder (Bl) in a patient with congenital adrenal hyperplasia. Note the dilated vagina (Vag), the cervix (*arrow*), and the bladder. ***B:*** Genitogram showing a high confluence (*arrow*) of the urethra and vagina with a long common urogenital sinus in a patient with congenital adrenal hyperplasia. ***C:*** Schematic of possible genitogram findings: I. and II. Urogenital sinus anomalies with two openings on the perineum (common urogenital sinus and rectum). III. and IV. Cloacal anomalies with 1 perineal opening. Note the low and high confluence of the urethra, vagina, and rectum (UVR). (Modified with permission from Dr Hardy Hendron.) Genitogram showing the common urogenital sinus.

Diagnostic Laparotomy or Laparoscopy

Occasionally, surgery is needed to delineate the internal genitalia and obtain a biopsy specimen of the gonads. It is indicated in patients in whom the biopsy result will influence sex assignment. In addition, surgery may be needed to remove streak or dysgenetic gonads in patients who are at risk for cancer (incomplete testicular feminization, Turner's Y variant, and mixed gonadal dysgenesis). Laparoscopic surgery has provided an alternative to open surgery in patients with intersex disorders. It can be performed safely in newborns and only requires 1–3 3-mm incisions for placement of the laparoscopic ports. Simple surgical procedures such as hernia repair, orchidopexy, and resection of discordant organs can be readily performed laparoscopically. More complex procedures may require 5-mm ports and larger instruments.

Sex Assignment

In the past, the baby born with ambiguous genitalia was considered incomplete until either a male or female sex was assigned. Unfortunately, a prompt but inappropriate assignment, although timely and comforting for family, physicians, nurses, and staff, can lead to more complex problems in the future. The issue of sexual determination remains complex. We reaffirm the teaching of our mentors by advocating an immediate and thorough attempt to make a definitive and accurate diagnosis. Fortunately, for most patients with ambiguous genitalia (ie, CAH), this can be accomplished. In patients where ambiguity remains after initial testing and the diagnosis cannot be made, or when the diagnosis is clear but sex assignment remains difficult, we would now advocate for a more cautious approach. Foremost, this would include a reversible or nonbinding sex assignment. Experience has shown that patients themselves may reassign their sex. For example, in cases of cloacal exstrophy or iatrogenic penile injuries, past treatment was based on the absence of an “adequate” phallic structure. These patients were converted from genetic males to females with surgical orchiectomy, removal of any excess male genitalia, vaginoplasty, and future hormonal treatment for breast development. Although surgical results can be anatomically successful, these women will not menstruate or have fertility potential, and their sexual function is not known. A number of these patients went through adolescence, have identified as females, and have not had major issues with their assigned discordant, genetic sexual identity. In contrast, some of these patients have subsequently identified with their genetic sex and demanded or reassigned their sex from female to male. In cases where the genotype does not match the phenotype, it is clear that surgical reconstruction from male to female does not guarantee a successful sexual identity.

The clinical experience exemplifies the complexity of sexual determination. It is clear that social factors, or the "nurturing" hypothesis, and biologic factors, or the "genetic" hypothesis, both play a role in determining our sexual identity. The nurturing hypothesis is based on the parent's perception of their child's genitalia. This perception will influence interactions such as naming, clothes, play orientation, and social organization. Clearly, how a parent perceives his or her child and the type of environment used to raise the baby is critical to the child's identity.

In contrast, the genetic hypothesis states that sexual identity is predetermined by the genetic makeup. Increasing laboratory evidence is accumulating to support the genetic hypothesis. For example, animal experimentation supports the concept of steroid or androgen imprinting of the brain. The human evidence supporting masculinization of the brain is supported by (1) women with virilizing CAH, (2) iatrogenic penile ablation in males raised as females, and (3) males with 5α-reductase deficiency who were raised as females. The common theme in these patients is the high level of in utero exposure to androgens theoretically masculinizing the brain and conferring a male identity. Another example of hormonal influence on sexual orientation can be found in women exposed to diethylstilbestrol. Human retrospective studies looking at these women reveal an increase in bisexual and homosexual orientation.

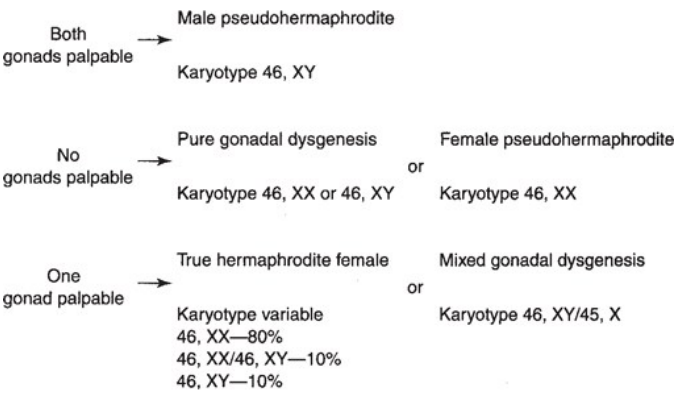
The process of sexual identity in both humans and experimental animals is not an all-or-none process, meaning that male and female characteristics exist as a continuum. For example, although the "garbage removal, plumbing, and TV-channel-flipping gene" seems to exist almost exclusively on the Y chromosome, these traits may also be found in the female sex.

Two issues must be separated when evaluating patients with intersex or ambiguous genitalia: (1) gender identity (Is the person's sense of identity male or a female?) and (2) sexual orientation. The incidence of discordant gender identity is approximately 1 in 30,000 males and 1 in 100,000 females. The incidence of same-sex orientation in both males and females is estimated to be approximately 5–10% of the population consistent with normal variation.

Practical Approach to the Diagnosis of Intersex

In the newborn period, patients with ambiguous genitalia can be approached in a logical fashion (Figure 43–11) (Lee et al, 2006). As noted earlier, history, physical examination, laboratory evaluation, and radiographic and in some cases surgical exploration are necessary to make an accurate diagnosis. Once the karyotype is known, along with the gonadal status, an appropriate test can lead to a diagnosis (Figure 43–11 and Table 43–5). Patients may also present at puberty (inappropriate or delayed development) with sexual differentiation abnormalities or later in life with infertility. The differential diagnosis for these disorders is diagrammed in Figure 43–12.

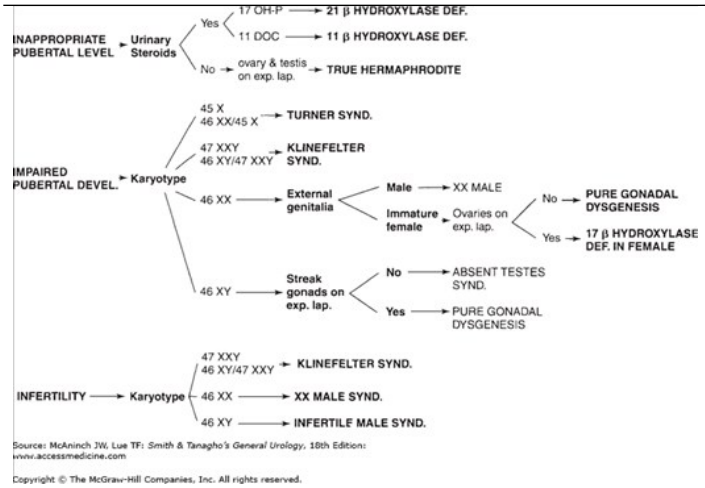
Figure 43–11.



Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Algorithm for initial workup of intersex based on physical examination and karyotype.

Figure 43–12.



Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Differential diagnosis of patients with inappropriate pubertal development, impaired pubertal development, and infertility. Def., deficiency; devel., development; DOC, 11-deoxycorticosterone; exp. lap., exploratory laparoscopy; 17 OH-P, 17 hydroxy progesterone; synd., syndrome.

Table 43–5. Differential Diagnosis for a Newborn with Ambiguous Genitalia.

	Common karyotype	Gonad status	Genitalia	Uterus	Urinary/Serum steroids
46,XX DSD (Female pseudohermaphrodite) (CAH)	XX	Ovary	Hypospadias	Present	Elevated
46,XY DSD (Male pseudohermaphrodite)	XY	Testes	Hypospadias/micropenis	Absent	Normal
45,X/46,XY DSD (Mixed gonadal dysgenesis	XY/XO	Streak dysgenetic	Hypospadias	Variable/rudimentary	Normal
Ovotesticular DSD (True hermaphrodite)	XX/mosaic	Ovotestis or ovary and testes	Hypospadias	Variable/rudimentary	Normal

Treatment of Specific Disorders

46,XX Dsd (Female Pseudohermaphrodites)

46,XX disorders of sex development (DSD) are characterized by a 46,XX genotype, nonpalpable gonads or normal ovaries, and variable degrees of virilization of the external genitalia.

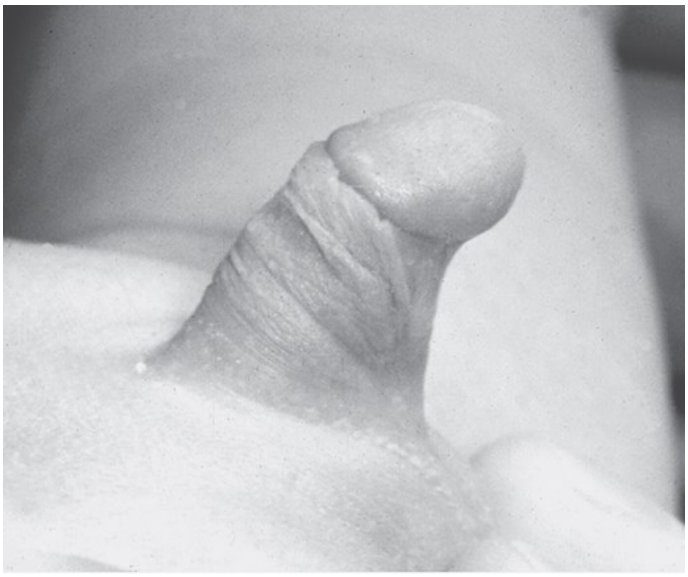
Congenital Adrenal Hyperplasia

CAH is the most common cause of female ambiguous genitalia or pseudohermaphroditism and accounts for approximately 70% of all patients with ambiguous genitalia. CAH accounts for >95% of the cases of female pseudohermaphroditism, with exposure to maternal androgens accounting for the remaining 5%. Mutations in one of five genes result in impaired cortisol secretion, which in turn causes excess secretion of adrenocorticotropic hormone (ACTH) and consequently adrenal hyperplasia (Speiser, 2007). Four of the five genes code for enzymes necessary for steroid hormone synthesis, and the fifth encodes for an intracellular cholesterol transport protein (StAR) (Figure 43–9). Deficiencies in 21α-hydroxylase and 11β-hydroxylase result in masculinization of the female fetus, while they have no effects on the genitalia of the male fetuses. In contrast, infants with deficiencies in 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and StAR have defects in both the synthesis of cortisol and steroid hormones. Affected males have varying degree of ambiguous genitalia due to deficiency in testosterone synthesis, while affected females may or may not be virilized.

21α-Hydroxylase deficiency is the most common cause of CAH, accounting for 90% of cases. The metabolites 17-hydroxyprogesterone and 17-hydroxypregnelone, which build up above the 21α-hydroxylase deficiency, are metabolized to androgens, resulting in virilization of the female external genitalia. Three forms of 21α-hydroxylase deficiency exist: classic, simple virilizing, and nonclassic. Each of these disorders is characterized by the activity level of the gene. Patients with the classic disease have both virilization and salt wasting, those with simple virilizing have masculinization without salt losing, and the nonclassic patients present after puberty with virilization.

In general, the classic form of 21α-hydroxylase deficiency exhibits the more severe forms of virilization (Figure 43–13). Impaired cortisol and aldosterone secretion leads to electrolytes and fluid losses, producing hyponatremia, hyperkalemia, acidosis, increased plasma renin, dehydration, and eventual vascular collapse unless recognized and treated. In affected males, deficiency in 21α-hydroxylase does not result in abnormal genitalia, and consequently, salt loss may occur unnoticed. Aggressive fluid resuscitation with normal saline should be instituted immediately and repeat serum electrolyte measurement should be obtained to monitor the progress of the resuscitation. Diagnosis is based on an elevated level of 17-hydroxyprogesterone in the urine and blood. After diagnosis and stabilization, replacement therapy should be instituted with glucocorticoids, mineralocorticoids, and salt. Regular measurement of serum electrolytes, renin, and ACTH helps to monitor the adequacy of hormonal replacement. Untreated patients with 21α-hydroxylase deficiency exhibit excessive growth, virilization, advanced bone age, and early closure of epiphyseal growth plates (Hughes, 2007).

Figure 43–13.



Patient with severe masculinization from congenital adrenal hyperplasia.

11β-Hydroxylase deficiency accounts for most of the remaining cases of CAH (approximately 9%). Patients with 11β-hydroxylase accumulate 17-hydroxyprogesterone as well as DOC and 11-deoxycortisol, which results in salt accumulation leading to hypertension. Patients with 11β-hydroxylase deficiency are more likely to present with hypertension secondary to the salt-retaining metabolites DOC and 11-deoxycortisol, in contrast to the hypovolemic shock associated with 21α-hydroxylase deficiency. Hypokalemia is also common secondary to an increase in mineralocorticoid activity.

Since CAH is hereditary, it is possible to counsel and offer treatment to families wishing further children. Maternal treatment with dexamethasone prior to the 10th week of gestation can significantly reduce the risk of masculinization of the female fetus (Miller, 1998). Standard prenatal treatment is 20 mg/kg two times daily beginning as soon as the pregnancy is confirmed (5th week of gestation) in a family with a positive history of CAH. At 9–10 weeks' gestation, chorionic villus sampling can confirm karyotype and test for the presence of the gene *CYP 21*, which is present in 21α-hydroxylase deficiency (90% of CAH cases). If the karyotype is XY or the CAH gene *CYP 21* is not present, the maternal dexamethasone treatment is stopped. Statistically, 50% of the fetuses will be male, and of the females, only 25% will be affected secondary to the recessive inheritance pattern of 21α-hydroxylase deficiency. Unfortunately, this will result in unnecessary prenatal steroid exposure in seven of eight fetuses with unknown long-term health consequences, such as hypertension. Although the short-term success of decreasing female virilization has been documented, long-term follow-up of fetuses exposed to steroids needs to be documented.

Maternal Hormonal Sources of Virilization

Maternal tumors are a rare cause of virilization of the female fetus. The most common type are luteomas of the ovary, which also virilize the mother. Diagnosis can be made by maternal blood samples and imaging studies (sonogram and magnetic resonance imaging). Maternal ingestion of medication is another rare cause of abnormalities in genital development (Table 43–6). Progesterone is a common agent being used early in pregnancy to prevent abortions as well as during in vitro fertilization treatments.

Table 43–6. Drugs that May Induce Disorder of Sex Development If Taken during Pregnancy.

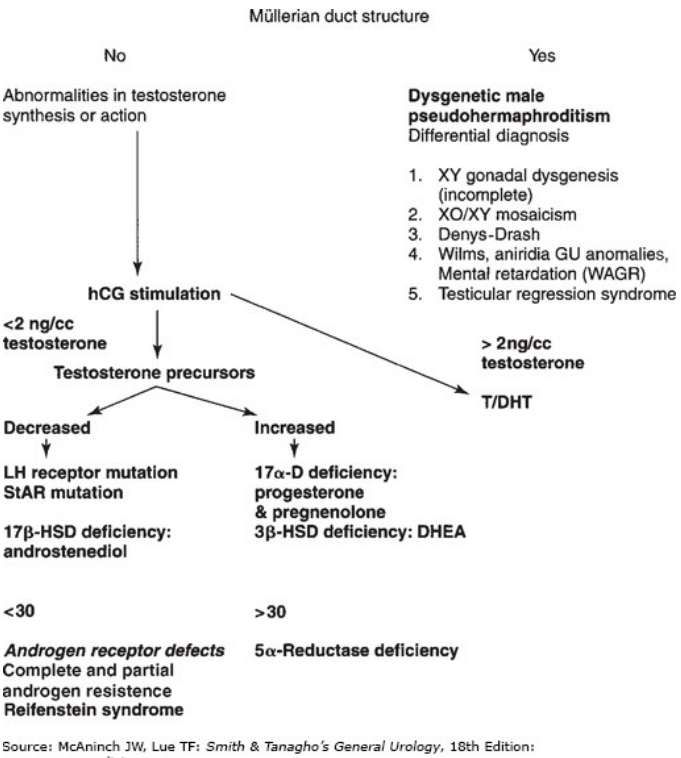
C21-steroid medroxyprogesterone acetate (progesterone)
Finasteride (Proscar)
Leuprolide acetate (Lupron)
Stilbestrol
Danazol
Norethynodrel
Ethisterone
Norethindrone

The female fetus that is exposed to high concentrations of progesterone can virilize secondary to direct action of progesterone on the AR. In the male fetus, hypospadias can develop by progesterone-inhibiting testosterone synthesis and downregulating the AR. A prenatal history of progesterone exposure should be elicited in the differential diagnosis of patients with abnormalities of the external genitalia.

46,Xy Dsd (Male Pseudohermaphrodites)

46,XY DSD are characterized by a 46,XY genotype, normal testes (usual palpable), and partial or complete masculinization of the external genitalia. The differential diagnosis is outlined in Figure 43–14.

Figure 43–14.



Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Differential diagnosis of patients with male pseudohermaphroditism. 17α-D, 17(α)-hydroxylase; DHEA, dehydroepiandrosterone; GU, genitourinary; hCG, human chorionic gonadotropin; HSD, hydroxy-steroid dehydrogenase; LH, luteinizing hormone; StAR, steroidogenic acute regulatory protein; T/DHT, testosterone/dihydrotestosterone.

Two forms of androgen resistance related to male pseudohermaphrodites are complete androgen insensitivity and partial androgen insensitivity.

Complete Androgen Insensitivity

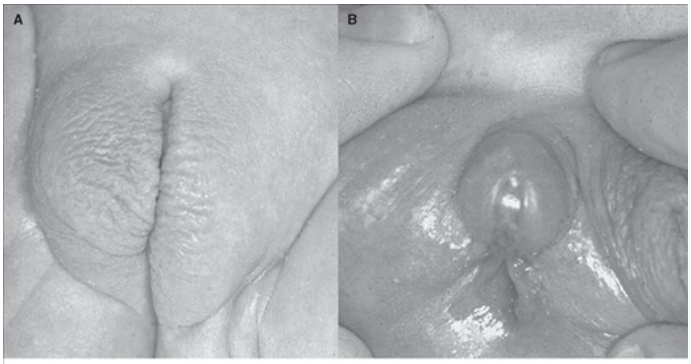
Androgen resistance ranges from partial to complete due to a defect in the AR. Patients with complete androgen resistance or androgen insensitivity syndrome (AIS) (previously called testicular feminization) have a 46,XY karyotype but have unambiguous female external genitalia, hypoplastic labia majora, a blind vaginal pouch, and an absent uterus (Wisniewski et al, 2000). Since a functional AR is necessary for the development of axillary and pubic hair, complete AIS patients have sparse to nonexistent hair growth in these areas. Complete AIS patients either inherit the disease by an X-linked recessive pattern or develop a spontaneous mutation that renders the AR nonfunctional. Patients with complete AIS appear to identify as females. Presumably, the functional defect in the AR also exists in the brain, preventing "masculinization." There is not enough long-term follow-up to assess issues with sexual identity in these patients.

Complete androgen resistance should be suspected in phenotypic females who present with an inguinal hernia that contains a testis (approximately 1% of all prepubertal females undergoing hernia repair) (Oakes et al, 2008). The most common presentation for complete AIS is amenorrhea in adolescent females. Breast development occurs in AIS patients secondary to the peripheral conversion of testosterone to estradiol from aromatase enzyme. After puberty, the testes have approximately a 10% risk of developing cancer, the most common tumor being a seminomatous germ cell. Because of the significantly increased cancer risk, removal of the gonads is recommended after postpubertal breast development. Alternatively, the gonads can be removed at the time of diagnosis, with estrogen replacement therapy initiated in the pubertal time period. Since the vagina may be inadequate in length, some patients may need augmentation procedures. Self-vaginal dilation is the most common technique, followed by vaginal augmentation procedures using skin grafts or bowel.

Partial Androgen Insensitivity

In contrast to complete AIS, patients with partial androgen resistance may have external genitalia ranging from mild to severe hypospadias (with or without cryptorchidism) to micropenis or clitorimegaly with partial labial fusion (Figure 43–15) (Griffin et al, 1995). The testes may be located in the labia, inguinal canal, or abdomen. The testes are histologically normal before puberty. However, after puberty, spermatogenesis is usually absent and there is Leydig cell hyperplasia. The testes are predisposed to malignant transformation in 4–9% of the patients (Fallat and Donahoe, 2006).

Figure 43–15.



Partial androgen receptor defect resulting in severe hypospadias with curvature (***A***) and a small phallus (***B***).

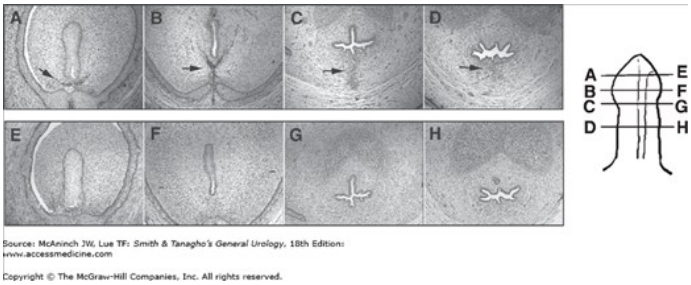
The defect in partial androgen resistance is typically due to a single base pair mutation in the AR. Inheritance may be X-linked, autosomal recessive, or from a spontaneous mutation. Interestingly, the same genetic defect within a family may have a different phenotypic expression. The variability of phenotypic expression makes counseling difficult in affected families.

In patients with partial androgen resistance, the sex of rearing depends on the degree of androgen resistance and the degree of genital ambiguity. In patients who respond to high-dose androgen therapy (2 mg/kg initially followed by 4 mg/kg) with phallic growth, the sex of rearing as male has been successful. Genital reconstruction repairing the hypospadias and undescended testes is performed at an early age. Patients who have a poor response to androgen stimulation fall into a difficult category of intersex. In the past, patients who were raised as females had feminizing genital surgery and gonadectomy typically in the first year of life. At the time of puberty, estrogen replacement is instituted. Presumably in partial androgen insensitivity, sexual identity is influenced by the effects of androgens on central imprinting. A discord may exist between the external genitalia that partially responds to androgen stimulation and the effects of androgens on determining sexual identity in the brain (Zucker, 2003). The fact that some patients with severe hypospadias and a small phallus have had difficulty with sexual identity in adulthood makes sex assignment difficult. Presently, it seems reasonable to delay irreversible surgery until after the patient has developed a sexual identity and can drive the decision for reconstructive surgery.

5a-Reductase Type 2 Deficiency

5α-Reductase type 2 deficiency is an autosomal recessive transmitted disorder affecting the formation of the male genitalia (Wilson et al, 1993). 5α-Reductase is responsible for the conversion of the less potent testosterone to the five to ten times more potent DHT. Type 2 5α-reductase predominates in the tissue of the external genitalia and the prostate, whereas type 1 5α-reductase localizes to the skin and nongenital tissues. Numerous mutations have been described in the 5α-reductase type 2 gene consistent with the variation in clinical spectrum seen in patients with this defect. Immunohistochemical localization of 5α-reductase type 2 reveals that the enzyme is located in the midline urethral seam (Figure 43–16) (Kim et al, 2002). The midline seam localization is consistent with the formation of hypospadias in patients with 5a-reductase type 2 gene defects in that the epithelial edges of the urethral seam would fail to fuse, resulting in hypospadias.

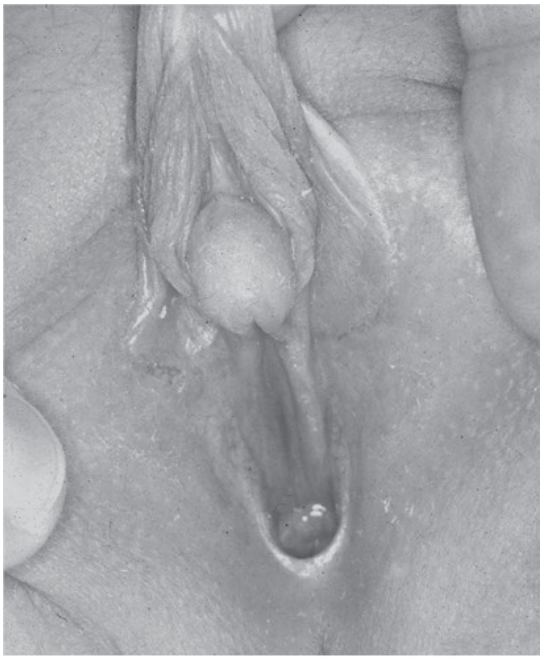
Figure 43–16.



Immunohistochemical localization of 5α-reductase type 2 (***A–D***) and the androgen receptor (AR) (***E–H***) in the same human fetal penis at 16.5 weeks of gestation (reduced from 25×). Note the strong expression of 5α-reductase type 2 along the urethral seam area (*arrows*).

Clinically, patients with 5α-reductase type 2 present with a small phallus, severe hypospadias, bifid scrotum, and a residual prostatic utricle or blind-ending vaginal pouch (Figure 43–17). The testes are often undescended in the inguinal canal. Untreated patients will typically virilize during puberty when elevated levels of the less potent testosterone either overwhelm the functioning androgen gene or the functioning 5α-reductase type 1 enzyme cross-reacts with the excess testosterone, converting it to DHT.

Figure 43–17.



A patient with 5α-reductase type 2 deficiency. Note severe hypospadias with a small phallus, bifid scrotum, and visible prostatic utricle or blind-ending vaginal pouch.

Sexual identity appears to be intact for karyotype XY males with 5α-reductase type 2 deficiency, presumably from an intact masculinization of the brain. In specific geographic areas such as the Dominican Republic, where the incidence of 5α-reductase type 2 deficiency is relatively high, it is generally accepted that these children will change from an initial "in-between" sex to a male sexual identity at the time of puberty.

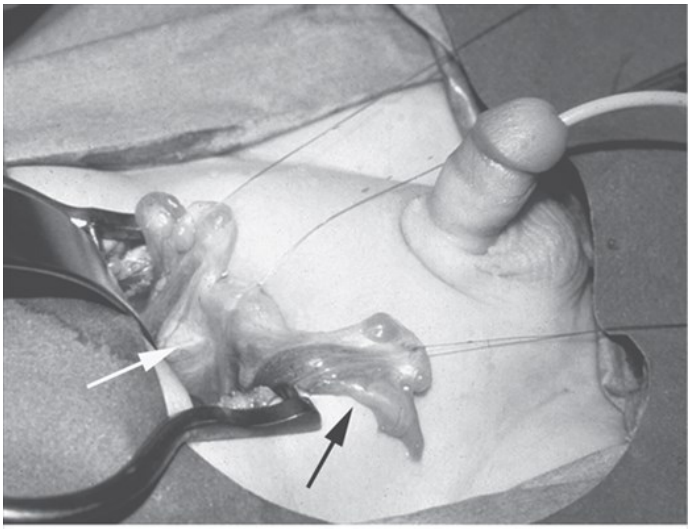
The diagnosis of 5α-reductase type 2 deficiency should be considered in severe phenotypes of hypospadias, especially with associated scrotal anomalies and undescended testes. Diagnosis is based on an increase in ratio of testosterone to DHT. Since these patients have a small phallus, attempts at enlargement with DHT cream are reasonable, although DHT is difficult to obtain in the United States. Reconstructive surgery for the hypospadias and undescended testes is indicated. Fertility has not been reported in patients with 5α-reductase type 2, although sperm production has been documented.

Persistent MüLlerian Duct Syndrome

Müllerian-inhibiting substance or factor (anti-Müllerian duct hormone) causes regression of the structures that would have formed the uterus, fallopian tube, and upper part of the vagina. Defects in the MIS gene or MIS receptor result in retained Müllerian structures typically inherited as an autosomal recessive defect. Male siblings of affected patients, especially with cryptorchidism, should undergo screening; they have a 25% chance of being affected (Rey et al, 1999).

Clinically, patients with persistent Müllerian duct syndrome present, unexpectedly, at the time of surgery for cryptorchidism (Figure 43–18). Hence, the alternate name for persistent Müllerian duct syndrome is hernia uterine inguinale. Within the hernia sac, a fallopian tube, uterus, or both are found attached to the testicular cord structures. What makes the treatment difficult is that these structures and hence the diagnosis are found unexpectedly at the time of surgery for cryptorchidism. If persistent Müllerian duct structures are found during orchiopexy, it is reasonable to abort the procedure until a correct diagnosis can be determined. At the initial exploration, a clear description of gonad and surrounding Müllerian structures should be documented, with a biopsy specimen of the gonad taken and a karyotype obtained.

Figure 43–18.



Hernia uterine inguinale or persistent Müllerian duct syndrome. Note the presence of a fallopian tube (*black arrow*) and uterus attached (*white arrow*) to the testicular cord structures.

Once a definitive diagnosis is made, reconstructive surgery can then be performed. Separation of inappropriate Müllerian structures from the cord without disturbing the vas deferens, the testicular artery, or both is the goal; however, this may be impossible if the vas runs through the Müllerian structures, which is a common outcome. Fertility is usually impaired in patients with persistent Müllerian duct syndrome even though testosterone levels may be normal. Whether this is a consequence of primary gonadal dysfunction or secondary to the cryptorchid testes is controversial. Efforts should be made to remove the Müllerian structures and deliver the testes into the scrotum or at least a palpable position in the groin for subsequent cancer surveillance. Testes cancer has been reported in 2–10% of patients. In patients where the testes remains in the abdomen or cannot be separated from the Müllerian structures, orchiectomy is indicated.

Abnormal Gonadal Function Syndromes

45,X Dsd (Turner's Syndrome)

Turner's syndrome is relatively common, occurring in 1 in every 2000 female births. The genotype in patients with Turner's syndrome is a complete or mosaic X monosomy, 45,X, or 45,X/46,XX) (Loscalzo, 2008). Turner stigmata consist of a web neck, shield chest, aortic valve defects, coarctation of the aorta, horseshoe kidney, short stature, and absent puberty. During fetal development in patients with Turner's syndrome, the ovaries develop but subsequently degenerate to streak gonads. The streak gonads are not at risk for cancer (unless Y chromatin material is present) and therefore do not need to be removed. Therapy is directed toward growth augmentation with growth hormone therapy in childhood. Subsequently, estrogen replacement is begun in late adolescence so as not to interfere with maximum growth.

46,XX Dsd Complete Gonadal Dysgenesis

Patients with 46,XX complete gonadal dysgenesis are typically diagnosed following a workup for delayed puberty or primary amenorrhea. Patients have a normal female phenotype without the stigmata of Turner's syndrome, normal external and internal Müllerian structures, and bilateral streak gonads. Sexual identity is female. Unlike patients with 46,XY gonadal dysgenesis, risk of tumor formation is rare and treatment is directed at hormonal replacement, with removal of the streaks gonads unnecessary.

46,Xy Dsd Gonadal Dysgenesis (Swyer's Syndrome)

Patients with 46,XY gonadal dysgenesis are characterized by absent testicular function in the presence of a Y chromosome. Classically, patients with 46,XY gonadal dysgenesis have a female phenotype. Patients come to medical attention if the prenatal karyotype (XY) is discordant with the child's phenotype (female), delayed puberty, amenorrhea, or precocious puberty from a hormonally functional gonadal tumor. The incidence of gonadal tumors is as high as 60%, with gonadoblastoma being the most common, although dysgerminomas, seminomas, and nonseminomatous germ cell tumors have also been reported.

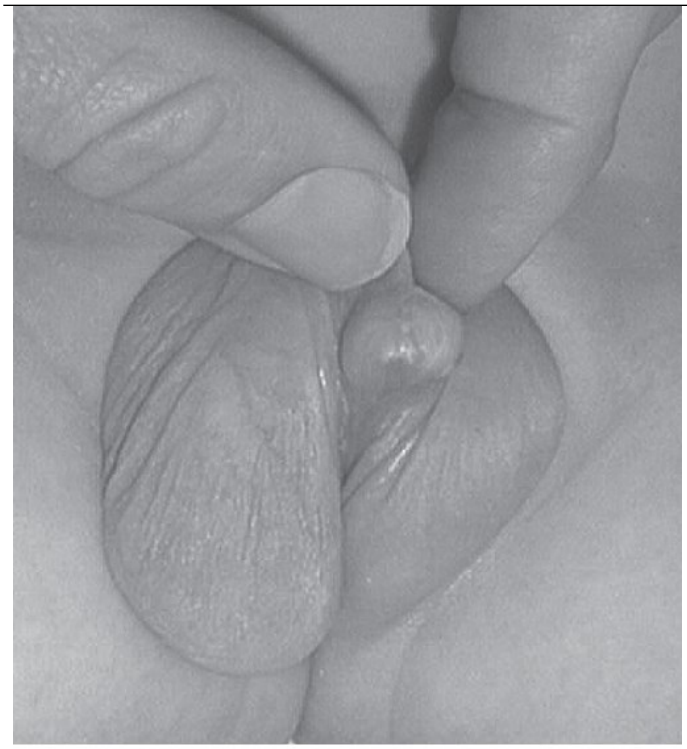
In pure XY gonadal dysgenesis, Müllerian duct structures usually are present secondary to failure of MIS secretion, and Wolffian duct structures are vestigial or absent secondary to lack of testosterone secretion. Laboratory analysis reveals female levels of baseline testosterone with no increase in response to hCG stimulation. Surgical exploration reveals streak gonads, fallopian tubes, and a uterus. With a 60% chance of tumor, the gonads need to be removed once the diagnosis is confirmed. These patients should be raised as females with estrogen replacement at the time of puberty.

45,X/46,Xy Dsd (Mixed Gonadal Dysgenesis)

Patients with mixed gonadal dysgenesis usually have a 45,X/46,XY, 46,XY, or other mosaic karyotype. They typically have one streak and one dysgenetic testis. Most children with mixed gonadal dysgenesis have incomplete virilization resulting in ambiguous genitalia or hypospadias with cryptorchidism. The other classic presentation is a mosaic genotype diagnosed on prenatal amniocentesis (Chang et al, 1990). Interestingly, the subsequent phenotype of patients with a prenatal karyotype of 45,X/46,XY is 90% normal male external genitalia. However, with a prenatal genotype of 45,X/46,XY, the patient is at risk for progressive gonadal changes leading to fibrosis and decreased fertility and low testosterone levels. The incidence of gonadal tumors does not seem to be increased. Most notably, 20% of these children have mental retardation or autism.

In patients who present with ambiguous genitalia, one gonad is typically palpable in the scrotum or inguinal canal and the other gonad (streak) is nonpalpable. The phallus size is typically small with a proximal or more severe hypospadias (Figure 43–19). Testosterone levels are normal with an appropriate response to hCG. MIS levels are usually normal. At surgery, the dysgenetic gonad (streak) may grossly appear normal but have microscopic abnormalities such as hypoplastic tubules surrounded by ovarian or fibrotic stroma. Variable Müllerian duct structures, such as fallopian tubes and uterus, are present depending on the degree of gonadal dysgenesis. On biopsy, the contralateral gonad in the scrotum or inguinal canal is either a normal or dysgenetic testis. In patients with mixed gonadal dysgenesis, the risk of gonadoblastoma is 15–30% (Levin, 2000). Gonadoblastoma is a steroid hormone–secreting gonadal tumor composed of large germ cells, Sertoli cells, and stromal derivatives. The incidence of gonadoblastoma appears to be higher in more undervirilized patients and the most common associated karyotype is 46,XY. Sixty percent of gonadoblastomas arise in an indeterminate gonad, 22% in streak gonads, and 18% in dysgenetic cryptorchid testis. Two cases occurring in a testis located in the scrotum have been reported. One-third of the patients have bilateral disease. Sixty percent of gonadoblastomas are associated with subsequent malignant germ cell tumor (germinoma, seminoma, and dysgerminoma but also embryonal teratoma, embryonal carcinoma, endodermal sinus tumor, or choriocarcinoma). Metastases develop in 10% of patients with germinomas arising within the gonadoblastoma.

Figure 43–19.



Presentation of mixed gonadal dysgenesis with ambiguous genitalia and a unilateral palpable gonad on the right side.

In children who are undervirilized, female sex assignment is an option, and the streak and dysgenetic gonads should be removed at the time of diagnosis due to increased risk of malignancy. Hormonal replacement with estrogen will be necessary during adolescence. If male gender is assigned, management of the scrotal testis is controversial, ranging from serial observation to surveillance biopsy. In the virilized patients who are raised as males, the testis will inevitably reveal poor hormonal and fertility potential (Woodhouse, 2001). These patients will require testosterone supplementation in adulthood (Birnbacher et al, 1999).

In 5% of patients, mixed gonadal dysgenesis is associated with Wilms' tumor, ambiguous genitalia, and progressive glomerulopathy known as the Denys-Drash syndrome. Wilms' tumor occurs in the first 2 years of life and is often bilateral. Classic presentation is an infant with ambiguous genitalia, hypertension, and nephrotic syndrome.

17b-Hydroxysteroid Dehydrogenase Deficiency

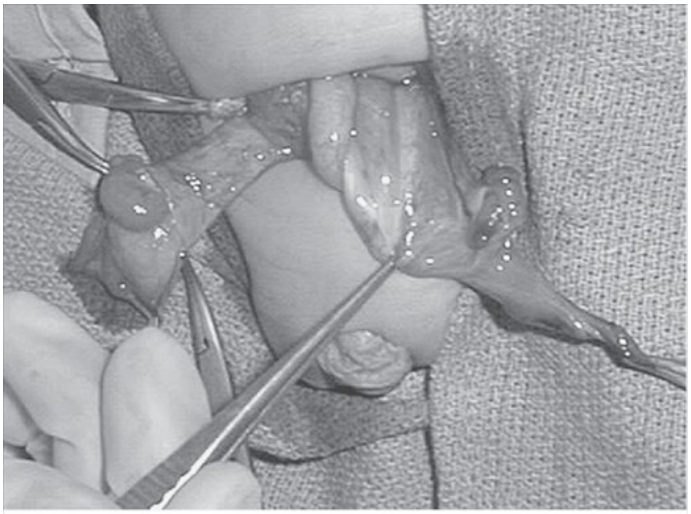
Patients with a defect in the enzyme 17β-hydroxysteroid dehydrogenase do not efficiently convert androstenedione to testosterone. 17β-Hydroxysteroid dehydrogenase is predominantly located in the testes. The rare disorder of 17β-hydroxysteroid dehydrogenase deficiency is inherited via an autosomal recessive pattern. This disorder is indigenous to the Arab population of the Gaza strip in the Middle East. Clinical presentation in a patient with XY genotype is mild virilization of the external genitalia, with clitoral hypertrophy, and a blind-ending utricle (vagina). The testes are undescended in the abdomen or inguinal canal or descended into the labioscrotal folds. If the virilization is mild, the diagnosis becomes apparent at puberty, with penile growth and male secondary sexual characteristics. At puberty, the increased levels of androstenedione are converted by nongenital, nonmutant 17α-hydroxysteroid dehydrogenase to testosterone. These patients may also present with gynecomastia at puberty by the peripheral conversion of androstenedione to estradiol by aromatase. Diagnosis is based on an increased ratio of androstenedione to testosterone postpubertal or in the prepubertal state in response to an hCG-stimulation test.

If the diagnosis is suspected in infancy, treatment with testosterone, reconstruction of the hypospadias, and male sex assignment are indicated. At puberty in the Gaza strip, gender conversion from female to male is common practice. Long-term outcomes of patients raised as females initially and reassigned to males at puberty await documentation.

Ovotesticular Dsd (True Hermaphroditism)

True hermaphroditism is defined as the presence of both ovarian and testicular tissue within the same individual (Figure 43–20). The most common karyotype in patients with true hermaphroditism is 46,XX (predominately in African Americans), followed by 46,XY/46,XX mosaicism. The latter karyotype in a patient with ambiguous genitalia strongly suggests the diagnosis of true hermaphroditism. Only 7% of patients with this disorder have a 46,XY karyotype. Interestingly, not all true hermaphrodites express the SRY gene, suggesting that non-SRY genes play a role in the development of the testes in these patients.

Figure 43–20.



Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Finding at the time of surgical exploration in a true hermaphrodite. On the patient's right side, note the testes, and on the left, note the fallopian tube, uterus, and biopsy-proven ovary.

In patients with true hermaphroditism, the gonads are a combination of ovotestis, ovaries, or testis. The most common configuration is ovotestis/ovary in 35%, followed by bilateral ovotestis in 25%, ovary/testes in 25%, and ovotestis/testes in the remaining 15%. One or both gonads are palpable in at least 60% of the patients. For unexplained reasons, the testis is more likely to be found on the right side. The testis and ovaries are located in their respective normal position, and the level of descent of the ovotestis is dependent on the amount of testicular tissue. While ovarian histology and function may be normal, testicular histology and function is usually abnormal. Ovotestis can be bilobar in configuration, with the ovarian and testicular tissue relatively separate, or the ovarian and testicular tissue may be intermingled and difficult to surgically separate. At the time of diagnosis, deep biopsies are necessary to determine the histologic status of the gonad. The internal structures tend to correlate with the type of gonad. Approximately 80% of true hermaphrodites will have a functional or rudimentary uterus. The uterus may be found in the abdomen or associated with an inguinal hernia. In patients with normal uterine structures and ovarian histology, fertility and normal pregnancies have been reported.

The external genitalia are usually ambiguous, although 60% of patients are masculinized, with a well-developed hypospadiac phallus. The hypospadias can be severe perineal or penile scrotal with incomplete fusion of the labioscrotal folds. The degree of masculinization is dependent on the amount of functional testicular tissue present. In childhood, testicular tissue has been documented to have normal spermatogonia. With maturation, however, testicular fibrosis occurs, with fertility in males a rare event. Testicular tumor is uncommon, occurring only in 1–2% of the patients.

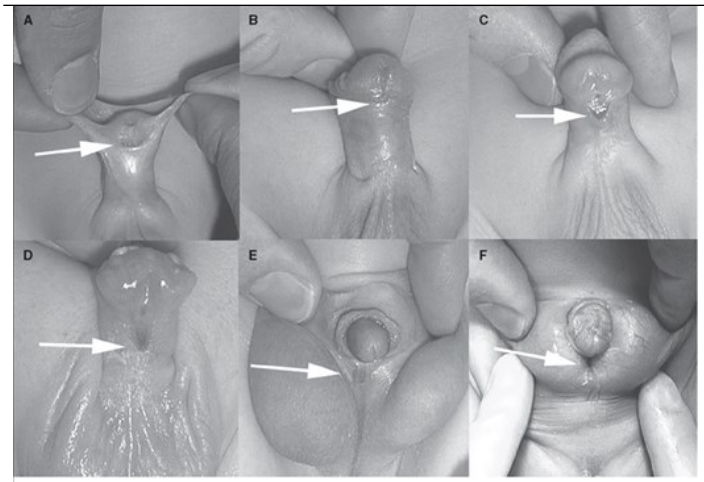
The diagnosis of true hermaphroditism should be suspected in patients with virilized ambiguous genitalia who have a 46,XX (African American) or mosaic genotype 46,XX/46,XY associated with the finding of Müllerian structures. Diagnosis is confirmed by gonadal biopsy confirming the presence of both ovarian and testicular tissue. After a decision regarding sex gender assignment has been made, gonadal tissue inappropriate for sex gender assignment should be removed. In patients who are raised as females, removal of all functioning testicular tissue is critical to prevent virilization at puberty. Surgical correction of the urogenital sinus to expose the vagina is necessary. In patients raised as males—who account for approximately 30% of all true hermaphrodites—the hypospadias and undescended testes should be reconstructed. In males, since testicular failure is common at puberty, testosterone supplementation may be required.

Unclassified Forms of Abnormal Sexual Development

Hypospadias

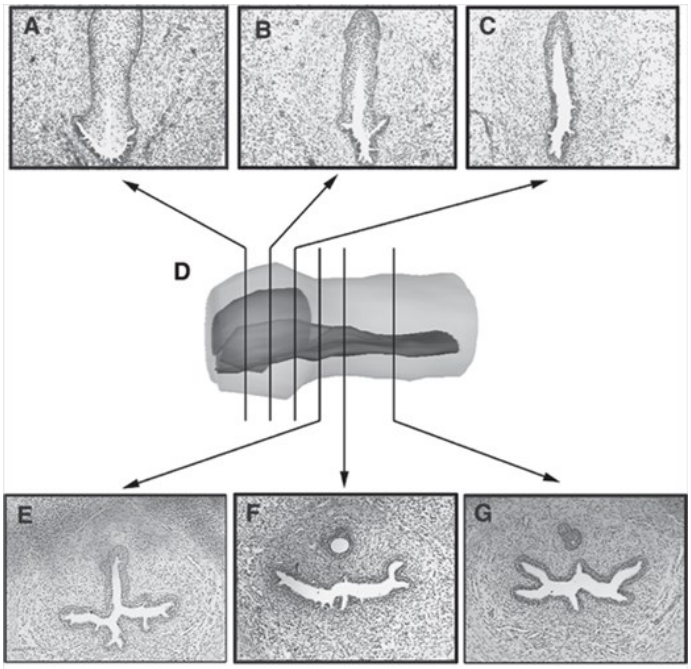
Hypospadias except in the most severe situation is not a form of DSD (intersex) (Figure 43–21) (Baskin and Ebbers, 2006). The etiology can be defined in less than 5% of patients. This leaves most cases without a defined etiology. The variable expression of the AR in the ventral versus the dorsal urethra may play a role in the etiology of hypospadias (Figure 43–22) (Baskin et al, 1998; Kim et al, 2002). Recent theories suggest an abnormality in closure of the midline urethral seam. Another possible etiology explaining the increase in incidence of hypospadias in western countries over the last 25 years is an increase in exposure to environmental endocrine disruptors (Baskin et al, 2001).

Figure 43–21.



The spectrum of hypospadias, which is not an ambiguous or intersex condition. ***A:*** Anterior, where the meatus is on the inferior surface of the glans penis. ***B:*** Coronal, where the meatus is in the balanopenile furrow. ***C:*** Distal, on the distal third of the shaft. ***D:*** Penoscrotal, at the base of the shaft in front of the scrotum. ***E:*** Scrotal, on the scrotum or between the genital swellings. ***F:*** Perineal, where the meatus is behind the scrotum or genital swellings.

Figure 43–22.



Androgen receptor (AR) expression in the human fetal penis at 16.5 weeks. A greater density of AR-positive cells is seen in the ventral portion of the urethral epithelium in the distal glans (***A)***, midglans ***(B)***, and proximal glans ***(C)***. In the distal ***(E)***, mid ***(F)***, and proximal ***(G)*** shaft of the penis, all portions of the urethral epithelium show the same density of expression. Three-dimensional reconstruction was performed to demonstrate the urethral AR expression pattern ***(D)***. Note the weaker density of AR in the dorsal aspect of the glanular urethra.

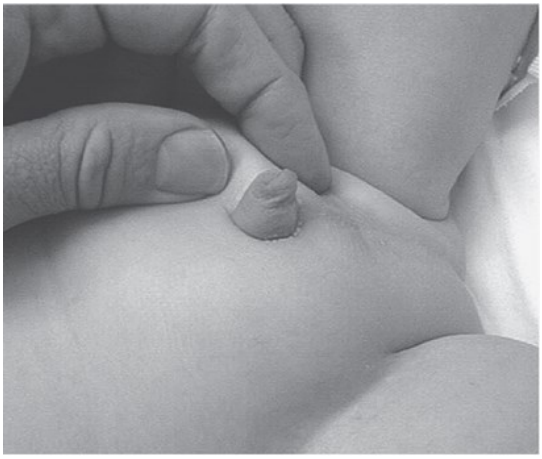
In controlled studies, most patients with hypospadias undergo successful surgical reconstruction and have acceptable long-term outcomes. Patients with hypospadias have an unambiguous male sexual identity. In severe forms of hypospadias with perineal or scrotal urethral openings, severe curvature and the phallus buried within the scrotum are the critical issues confirming the correct diagnosis. This is also the case for patients with hypospadias and a nonpalpable or undescended testis. If any doubt exists, patients with severe hypospadias, hypospadias in association with an undescended testis, or both, a karyotype should be checked to document genotype (McAleer and Kaplan, 2001). In severe cases of hypospadias where penile size is difficult to assess secondary to severe chordee, an hCG stimulation will assess the gonadal axis and

confirm an intact AR by eliciting penile growth.

Micropenis

A penis less than 2.5 cm in stretched penile length without hypospadias in a full-term male is defined as micropenis (Figure 43–23 and Table 43–4). Micropenis can be caused by multiple etiologies, the most common being fetal testosterone deficiency followed by partial defects in the AR or 5α-reductase enzyme (Table 43–7). Fetal testosterone synthesis can be divided into two categories: (1) primary testicular failure (Leydig cell) and (2) central failure. Central failure can be from congenital hypopituitarism or isolated gonadotropin deficiency. Patients with decreased fetal testosterone production either from (Fallat and Donahoe, 2006) Leydig cell failure or lack of Leydig cell stimulation from gonadotropin deficiency respond to treatment with supplementary testosterone enanthate intramuscular injections 25–50 mg each month for 3 consecutive months.

Figure 43–23.



Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

Micropenis. Normal corporeal bodies are palpable within the foreskin. The urethral meatus is at a terminal position within the glans. Stretched penile length is <2.5 cm in this full-term infant.

Table 43–7. Etiologies of Micropenis.

I. **Deficient testosterone secretion**
   a. Hypogonadotrophic hypogonadism
      1. Kallmann syndrome
      2. Prader-Willi syndrome
      3. Laurence-Moon syndrome
      4. Bardet-Biedl syndrome
      5. Rudd syndrome
   b. Primary hypogonadism (“Bum Gonads”)
      1. Anorchia
      2. Klinefelter syndrome
      3. Gonadal dysgenesis (partial)
      4. LH receptor defects (partial)
      5. Noonan syndrome
      6. Trisomy 21
      7. Robinow syndrome
      8. Bardet-Biedl syndrome
      9. Laurence-Moon syndrome
      10. Testosterone synthesis defects (partial)
II. **Defects in testosterone action**
   a. Androgen receptor defects (partial)
   b. 5α-Reductase deficiency
   c. Growth hormone/insulin growth factor-1 deficiency
   d. Fetal hydantoin syndrome
III. **Developmental anomalies**
   a. Aphallia
   b. Cloacal exstrophy
   c. Iatrogenic injuries
      1. Circumcision
      2. Trauma

Long-term outcomes of patients with micropenis have documented that final adult penile length is normal for >90% of patients treated with multiple short courses of testosterone enanthate. In addition, patients with micropenis identified with the male gender had normal erections, ejaculation, and orgasm. In rare patient who does not respond to testosterone stimulation, gender conversion to female had been advocated in the past. Presently, gender conversion would not be considered based solely on the small phallus size.

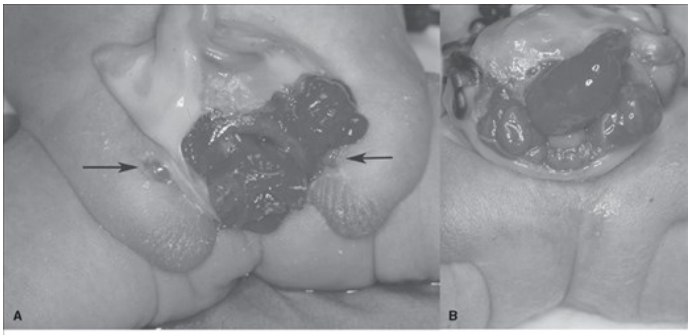
Reassignment to the female gender with removal of the gonads and feminizing genitoplasty in patients with penile agenesis, iatrogenic penile amputation, or circumcision injury had been standard treatment. In complete penile agenesis, the testicles are normal, corporeal bodies are absent, and the urethra opens into the anterior rectum or perineum. These patients have normal prenatal androgen levels, and hence, the brain has received signals for male gender identity (Wisniewski et al, 2001). The same is true for the rare patient who has a severe penile injury during circumcision. As in micropenis, gender conversion would now not be considered based solely on the absence or small size of the phallus. Penile reconstruction, although not technically ideal, may provide the best overall outcome.

Cloacal and Exstrophy Anomalies

In the past, patients with the most severe and rare form of lower abdominal congenital malformation, cloacal exstrophy (incidence of 1 in 200,000 live births), were usually left to die. Significant problems associated with surgical reconstruction of cloacal exstrophy include omphalocele; numerous gastrointestinal anomalies such as short gut, malrotation, duplication, duodenal atresia, and Meckel's diverticulum; and significant genitourinary anomalies such as separate bladder halves, upper-tract renal anomalies, and bifid genitalia. Patients with cloacal exstrophy can also have neurologic and orthopedic anomalies such as tethered cord, myelomeningocele, lower extremity paralysis, club-foot, and hip dislocation.

Historically, newborn males with cloacal exstrophy (Figure 43–24) were often gender converted to female as a result of inadequate genital development and the poor prognosis for surgically developing a normal male phenotype. In rearing genetic males as females, although the surgical reconstruction can match the assigned female phenotype, a new set of issues was created, such as the need for hormonal replacement with estrogen during adolescence and the issue of a nonmenstruating infertile female. In addition, the fetal and neonatal androgen imprinting on the brain does not seem to be reversible.

Figure 43–24.



A: Male with cloacal exstrophy. ***B:*** Female with cloacal exstrophy. In the male, note the split scrotal appearance and the small hemiphallus (*arrow*). In the female, the clitoral bodies/genitalia are not visible.

Because some of these XY, gender-converted females have self-reassigned their sex during adolescence to coincide with their genetic karyotype, there has been reevaluation of the practice of rearing genetic males as females. With the exact determinates of sexual identity not completely defined, a pragmatic approach is to delay any irreversible surgery such as orchiectomy or phallic removal/reduction in these patients. With modern surgical techniques and a multidisciplinary approach to their care, children with this complex disorder can have a normal sexual identity.

Surgical Management of Dsd

The surgical management of patients with intersex is undergoing a reevaluation. The determination of a patient's sexual identity is strongly influenced by the genetic karyotype and steroid/androgen action on the developing brain. The environmental and social impacts are certainly important but presently seem to have a less dominating influence.

We would advocate surgical management of patients with intersex when the diagnosis is clearly established and the long-term outcome for the diagnosis is favorable. Surgery falls into five categories: (1) diagnostic/biopsy, (2) gonadectomy and removal of inappropriate Müllerian structures, (3) clitoral reduction, (4) vaginoplasty, and (5) phallic reconstruction.

Diagnostic techniques have improved with the widespread use of laparoscopy to assess the morphology of the internal genital structures. Laparoscopic techniques allow the gonads and associated structures to be visualized and in some cases have a biopsy specimen taken without the need for a open incision. Once the diagnosis is established, it is possible to remove an inappropriate gonad, Müllerian remnant, or both via laparoscopic techniques.

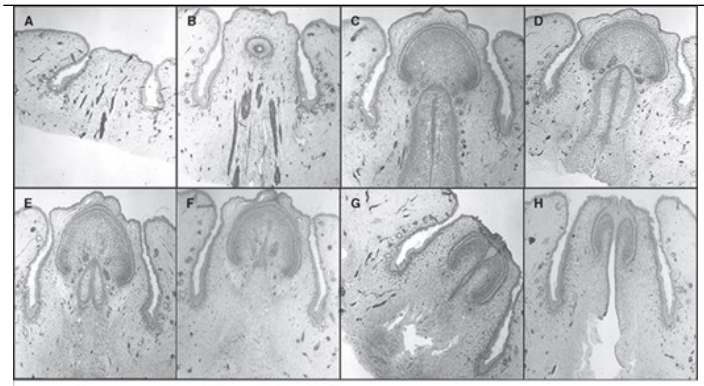
Clitoroplasty

Clitoroplasty is presently a controversial topic. No studies exist to clearly document whether androgen stimulation resulting in a large clitoris requires reduction or can be left intact. Clearly, surgery on the clitoral structures can result in nerve damage and removal of erectile tissue.

Historically, the enlarged clitoris/phallic structure has been dealt with by amputation (Gross and Crigler, 1966). Subsequently, more refined techniques such as recession clitoroplasty were developed where the entire clitoral organ is preserved by imbricating and burying the proximal corporeal shaft and excess glans clitoris. The disadvantage of the clitoral recession procedures may not become apparent until puberty, when the recessed corporeal bodies become enlarged and painful during sexual stimulation. This leads to the need for a procedure involving subtotal resection of the shaft of the clitoris with preservation of the glans.

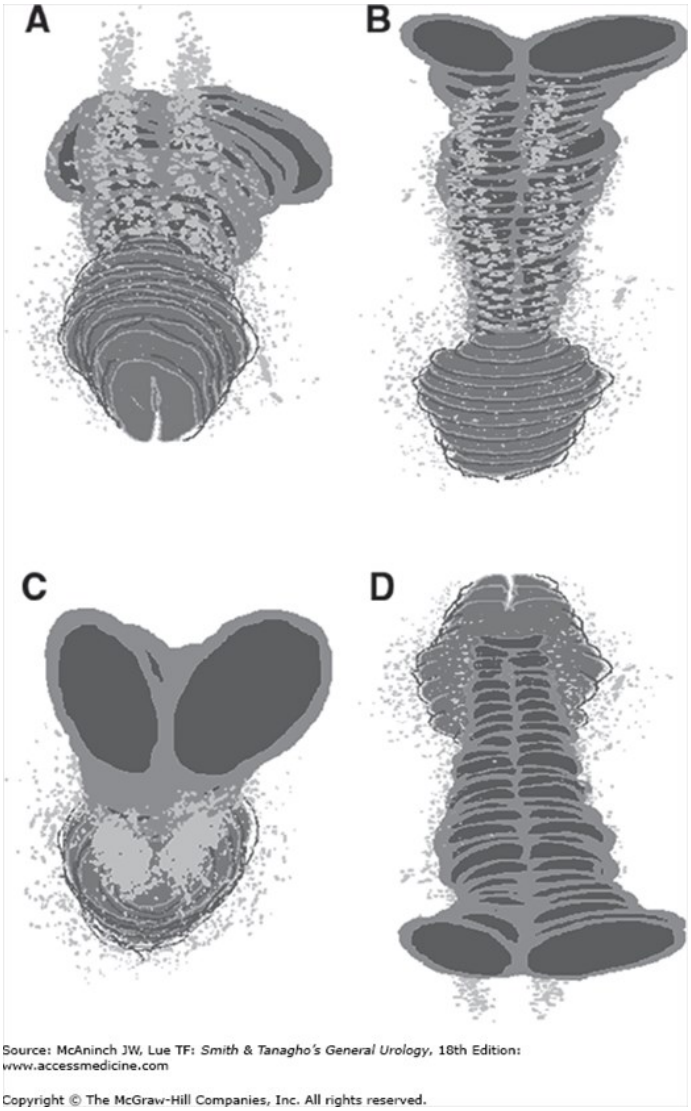
In cases where clitoroplasty is performed, the goal is to recreate the normal female anatomy. Presently, more conservative procedures have been employed to preserve both the sensory and cosmetic aspects of the clitoris. An understanding of normal female anatomy has benefited the design of reconstructive surgery in patients with CAH (Figures 43–25 and 43–26) (Baskin et al, 1999). A contemporary reduction clitoroplasty is based on anatomical observations from fetal anatomical dissections. Presently, the tunica of the corporeal body can be preserved to spare as much of the dorsal nerve as possible. The concept of lifting the dorsal nerve off the tunica at the 11 and 1 o'clock positions seems inconsistent with the fact that the nerves fan out extensively around the dorsal and lateral aspects of the clitoral body.

Figure 43–25.



Normal human fetal clitoris at 24 weeks' gestation (403) immunostained with the neuronal marker S-100 (dark stain). ***A:*** Clitoral hood, labia minora, and majora. ***B:*** Nerves on top of the erectile body and top of glans clitoris. ***C–E:*** Glans clitoris and erectile bodies. ***F–G:*** Lower part of glans clitoris with midline cleft. ***H:*** End of glans clitoris and vaginal introitus.

Figure 43–26.



Normal human fetal clitoris, 24 weeks' gestation. Four views of a computer-generated three-dimensional reconstruction (***A:*** top; ***B:*** bottom; ***C:*** back/top; ***D:*** bottom). Note

the pathway of the nerves (light gray) with a paucity of nerves on the bottom of the clitoris as well as in the top midline.

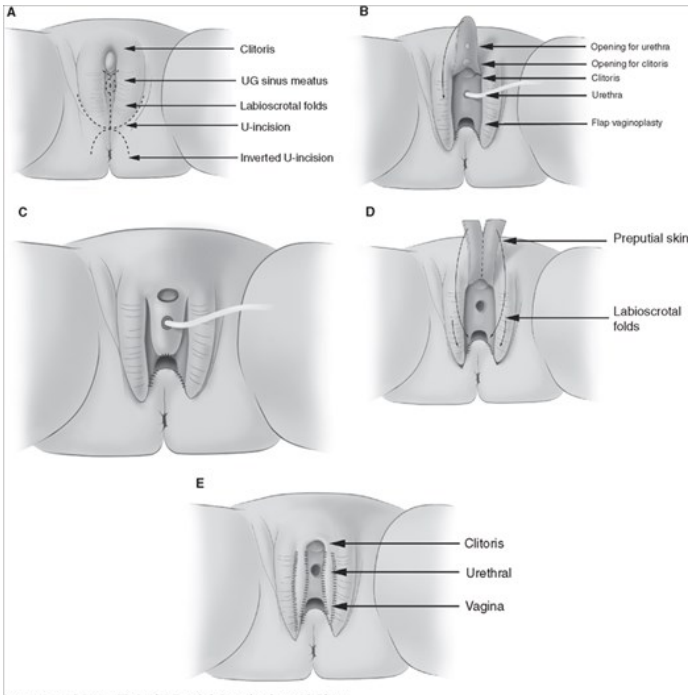
A second issue is the removal of erectile tissue. In severe cases of masculinization of the genitalia (Prader V), consideration may be given to reduce the amount of erectile tissue. Standard treatment was to amputate the erectile body of the clitoris at the pubic arch, leaving each crural body and the neurovascular bundle with a strip of dorsal tunica. The long-term effects of removing this erectile tissue on sexual function are unknown. In contrast, leaving too much erectile tissue has been reported to cause pain in patients at the time of puberty. This, however, may be from fixing the corporeal tissue to the pubic bone, a practice that is no longer advocated. A compromise is to incise the erectile body on the ventral surface at the 6 o'clock position away from the nerves and remove erectile tissue within the tunica to reduce the size of the erectile body, thereby preserving some erectile tissue and the nerves of the clitoris.

Vaginoplasty

The timing of vaginoplasty is also a controversial issue in genital reconstruction. The presence of a vagina is not necessary until puberty and initially only to allow the passage of menstrual fluids. Later the vagina is necessary for vaginal penetration, fertility, and, in most females, a healthy female sexual identity. This may not be the case for all females, for example, a woman with a small vagina and a female sexual identity with a female sexual preference may not desire a larger vagina. In patients with absent Müllerian structures (specifically a functional uterus) who have a female sexual identity, menstruation is not an issue and timing of vaginoplasty can be driven by the patient's wishes and motivation. In patients with a common urogenital sinus and hidden vagina, there are advantages and disadvantages of early surgery in the first year of life versus late surgery prior to puberty (Farkas et al, 2001). The advantage of early vaginoplasty is the closeness of the vagina to the perineum and the reported decreased bleeding in the early years of life. The major disadvantages are the smallness of the structures and that secondary surgery at the time of puberty may be necessary to correct vaginal stenosis. In contrast, delaying surgery has the advantages of operating on larger structures and the possibility that the patient can perform postoperative vaginal dilation to prevent stenosis (Hensle et al, 2006).

The type of vaginoplasty depends on the level of masculinization. For low urogenital sinus anomalies, a flap vaginoplasty will usually allow for an adequate introitus with separation of the urethra and vagina (Figure 43–27). For high urogenital sinus anomalies, partial urogenital mobilization and use of the elongated common urogenital sinus as an anterior vaginal flap may be necessary (Figure 43–28) (Rink and Cain, 2008). In the case of an absent vagina or a very short vagina, substitution vaginoplasty with bowel or skin grafting maybe required (Thomas and Brock, 2007). More recently autologous buccal mucosa has been successfully for used vaginal reconstruction (Samuelson and Baker, 2006).

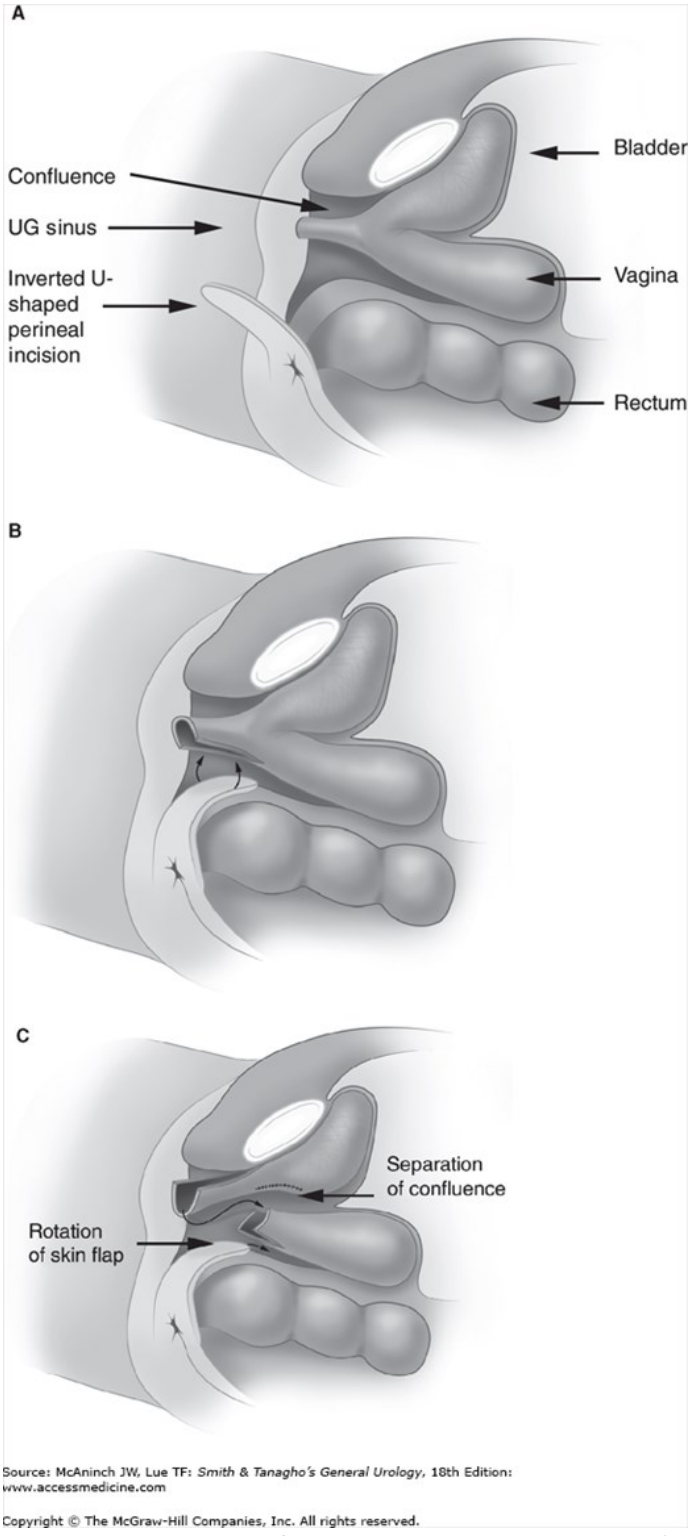
Figure 43–27.



Female external genitalia reconstruction in patients with a low confluence using a flap vaginoplasty. ***A:*** Surgical schematic of the perineum in patients with common urogenital sinus. ***B:*** The anterior flap for the vagina can be created using the phallic skin or the distal portion of the urogenital sinus. Two openings are created in the midline of the preputial skin flap to accommodate the clitoris and urethra. The preputial skin flap is then brought down and sutured to the anterior wall of the vagina. ***C:*** The completed repair. ***D:*** Alternatively, the preputial skin can be split in the midline and used for reconstruction of the vaginal introitus and the anterior vaginal wall. ***E:*** The completed repair. (Used with permission from Nguyen HT, Baskin LS: A child with ambiguous genitalia. In AUA Patient Management Problem, 2002. Decker Electronic

Publishing, Inc., 2002.)

Figure 43–28.



Partial urogenital mobilization for high urogenital sinus. ***A:*** The urogenital (UG) sinus is separated from the rectum posteriorly and the pubic bone anteriorly. ***B:*** The posterior skin flap (*arrows*) is assessed for length to reach the vagina. ***C:*** The confluence of the vagina and urethra (*arrow*) is separated. (Used with permission from Nguyen HT, Baskin LS: A child with ambiguous genitalia. In AUA Patient Management Problem, 2002. Decker Electronic Publishing, Inc., 2002.)

Phallic Reconstruction

Phallic reconstruction is a formidable task. Nevertheless, it is critical that reconstructive efforts continue in this area, especially for patients with penile agenesis or iatrogenic injuries and a XY genotype and functional AR. Several techniques have been devised, such as free microanastomosis, innervated radial forearm flaps, tubed abdominal flaps with a penile prosthesis, and rectus abdominus myocutaneous flaps. In the free radial forearm flap, the pudendal nerve is anastomosed to the lateral cutaneous nerve of the forearm. The radial artery and vein are anastomosed to the inferior epigastrics, the internal pudendals, or the femoral vessels. The major complications with these procedures are fistula, prosthesis erosion, and poor sensation. The technical nuances of microvascular anastomosis require that these procedures be performed in adolescents and adulthood. The psychological implications of relatively late reconstruction have not been determined. More recently, a technique to create a neonatal phallus from abdominal wall tissue has been described by De Castro et al (2007). Early results are encouraging but longer follow-up and the need for revision at the time of puberty will need to be determined. With newer tissue engineering techniques, better phallic reconstruction procedures may be on the horizon.

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