chapter 63

DISORDERS OF SEXUAL DIFFERENTIATION

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Disorders of sexual differentiation (DSD) resulting in what have previously been referred to as intersex disorders are among the most fascinating conditions confronting the pediatric urologist and surgeon. Our understanding of these conditions and their causes continues to evolve, but many questions remain. Even with a better understanding of the underlying etiology of these different conditions, optimal gender assignment and the timing of surgical reconstruction continue to be controversial.

NORMAL GENDER AND SEXUAL DIFFERENTIATION

An understanding of these conditions builds on a working knowledge of normal sexual differentiation. The most commonly accepted paradigm, described by Jost,[1] involves a stepwise process to gender and sexual development. The primary determinant is the chromosomal gender, which is established at fertilization when the sperm provides an X or Y chromosome to the ovum's X chromosome. Chromosomal gender determines gonadal gender, with XX resulting in ovarian development and XY resulting in testicular formation. Finally, the gonadal function determines the phenotypic gender, including internal and external physical and psychological features. Although this paradigm is a helpful cascade to explain gender development, as the actual genes and locations have been elucidated, the simple Y = male, No Y = female equations are not always valid.

Chromosomal Determination

The chromosomal gender determination is based on the Y chromosome. In the 1950s, research characterizing the male phenotype of Klinefelter's syndrome with a 47,XXY karyotype, and a female phenotype of Turner's syndrome with a 45,XO karyotype, discovered that the presence of the Y chromosome causes male gonadal development and the lack of a Y chromosome results in ovarian formation.[2,3] This was irrespective of a complete X chromosomal content. The theorized gene that was responsible for male gonadal development was termed the *testis-determining factor* (*TDF*).

Gonadal Development

The location of *TDF* was further elucidated with molecular techniques by studying individuals with chromosomes discordant with their phenotype: 46,XY females with a deletion of the *TDF* region and 46,XX males with Y chromosomal and *TDF* genetic material, presumably through gene translocation or other means. *TDF* was cloned and, based on genome mapping, its location was isolated to the short arm of the Y chromosome near the centromere at the distal aspect of the Y-unique region.[4] *TDF* was found to be a 35-kilobase pair sequence on the 11.3 subband of the gender-determining region of the Y chromosome (*SRY*). Interestingly, *SRY* appears to be expressed by the somatic cells from the urogenital ridge and not from germ cells.

The *SOX9* gene, located on the long arm of chromosome 17, has been identified as an additional gender-determining gene. It has been noted that a translocation involving the *SOX9* gene results in campomelic dysplasia, characterized by skeletal abnormalities and associated with 46,XY gender reversal. The *SRY* gene is thought to regulate the *SOX9* gene. Despite the presence of a functional *SRY* gene in this syndrome, a female phenotype develops in the majority of chromosomal males.[5,6]

In addition to the *TDF* and *SOX9* genes, other genes are also involved in gonadal development. The Wilms' tumor gene (*WT1*) appears to play a key role not only in renal development but also in testicular development. It is theorized that *WT1* regulates the interaction between the mesonephric ducts and germ cells, with early alteration of gene function resulting in testicular agenesis and later dysfunction resulting in aberrant testicular development (streak gonad or dysgerminomas). This tumor suppressor gene has been implicated in Denys-Drash syndrome involving testicular (mixed gonadal dysgenesis) and renal (Wilms' tumor) abnormalities.[7,8]

Fushi-Tarzu factor-1 (FTZ-F1) exerts its effect on gonadal development through its regulation of steroidogenic factor-1 (SF-1). The *SF1* gene is involved

with steroid hormone production and the production of müllerian-inhibiting substance (MIS) by the Sertoli cells of the testis that causes regression of the müllerian ductal system. Although FTZ-1 and SF-1 are also expressed in ovarian tissues, the timing and intensity of their effect are critical for normal gonadal development.[7,9]

Finally, the lack of an *SRY* gene alone does not impart normal female phenotypic and gonadal development, based on studies of 46,XY females with intact *SRY* regions. The *DAX1* gene, located on the short arm of the X chromosome, appears to be essential for the development of the ovary. The *DAX1* gene product appears to compete with the *SRY* gene product for a steroidogenic regulatory protein (StAR). Also, a dosage-sensitive element is important. Normally, the single *SRY* gene has a greater impact than a single *DAX1* gene and causes upregulation of StAR. In those chromosomal abnormalities in which more than one *DAX1* gene is present, however, downregulation of StAR occurs, testicular development is inhibited, and ovarian formation is promoted. As in the case of Turner's syndrome, however, these primordial ovaries develop into streak gonads. Likely, other genes are also important for normal ovarian development.[10-12]

Phenotype Development

Development of the internal ductal structures is dependent on hormone secretion by the developing gonads (Table 63-1). In the absence of functioning testicular tissue, the female internal müllerian duct structures develop. The presence of a functioning testis results in male internal wolffian duct development. This differentiation is mediated by the production of testosterone from the testis. Testosterone promotes wolffian duct development along with MIS, which results in regression of the müllerian duct structures. This is a paracrine effect and therefore results in gonad specific ipsilateral ductal differentiation. This effect is likely dependent on high concentrations of androgen produced by the physically proximate gonad. Decreased levels of MIS by an abnormal testis or streak gonad result in ipsilateral müllerian development. This occurs despite regression of the müllerian ducts on the contralateral side with normal testicular MIS production. Conversely, systemic administration of androgen does not result in male ductal development in a female fetus.

Table 63-1 Derivation of the Urogenital System

Wolffian Duct (Mesonephric Duct)	Urogenital Sinus	Müllerian Duct (Paramesonephric Duct)
Male:	*Male:*	*Male:*
Epididymis	Bladder	Appendix testis
Vas deferens	Prostate	Prostatic utricle
Seminal vesicles	*Female:*	*Female:*
Female:	Bladder	Vagina (upper third)
Epoöphoron	Distal vagina	Uterus
Gartner's ducts		Fallopian tubes

MIS functions as a suppressor of müllerian duct development. It is thought that MIS acts by inhibiting the effect of growth factors on the müllerian ducts. MIS is produced by the Sertoli cells in the testis and is a specific marker for functioning testicular tissue in infancy. At puberty, MIS production in the male declines, but it increases in the female. In its absence, the müllerian structures develop by default. The concentration and timing of MIS secretion appear to be critical. Secretion occurs during week 7 of gestation. By week 9, the müllerian ducts become insensitive to MIS.[11]

External genital development follows a similar path (Fig. 63-1). In the absence of testosterone and, more important, its metabolite dihydrotestosterone (DHT), the external genitalia develop into the female phenotype. The male and female phenotypes are identical until week 7. In the male, testosterone production by the testicular Leydig cells surges at 7 weeks and remains elevated until week 14 of gestation. Testosterone is converted to DHT by 5α-reductase in the tissues of the genital skin and urogenital sinus. The testosterone-binding receptor has a four to five times higher affinity for DHT than testosterone and serves to amplify the effect of testosterone on the developing external genitalia. In the absence of 5α-reductase, the internal wolffian ducts are preserved but the external structures are feminized.

After birth, neonatal testosterone levels in a male surge in response to the loss of feedback inhibition by maternal estrogens and the subsequent rise in neonatal luteinizing hormone (LH) production. This testosterone production peaks around the second to third month of life. By 6 months, the levels remain identical in males and females until puberty. Through these surges, it appears that androgen imprinting may occur on susceptible tissues, including those of the genital organs, but also on sensitive tissues in the brain related to male-type behaviors and gender orientation. This early exposure may determine how these tissues respond to subsequent androgen exposure during puberty and adulthood.

ABERRANT GENDER DEVELOPMENT

Incidence

In North and South America and Western Europe, congenital adrenal hyperplasia (CAH) is the most common cause of neonatal ambiguous genitalia, accounting for approximately 70% of cases.[13,14] The overall incidence is approximately 1 in 15,000 live births. The rate is much higher in stillborns and in certain regional populations (Yupic Eskimos and the people of La Réunion, France).[15] In the United States, mixed gonadal dysgenesis is the next most common intersex disorder, with ovotesticular DSD (true hermaphroditism) the third most common. In other areas of the world, different disorders predominate. Ovotesticular DSD is the most common intersex disorder in South Africa.[16]

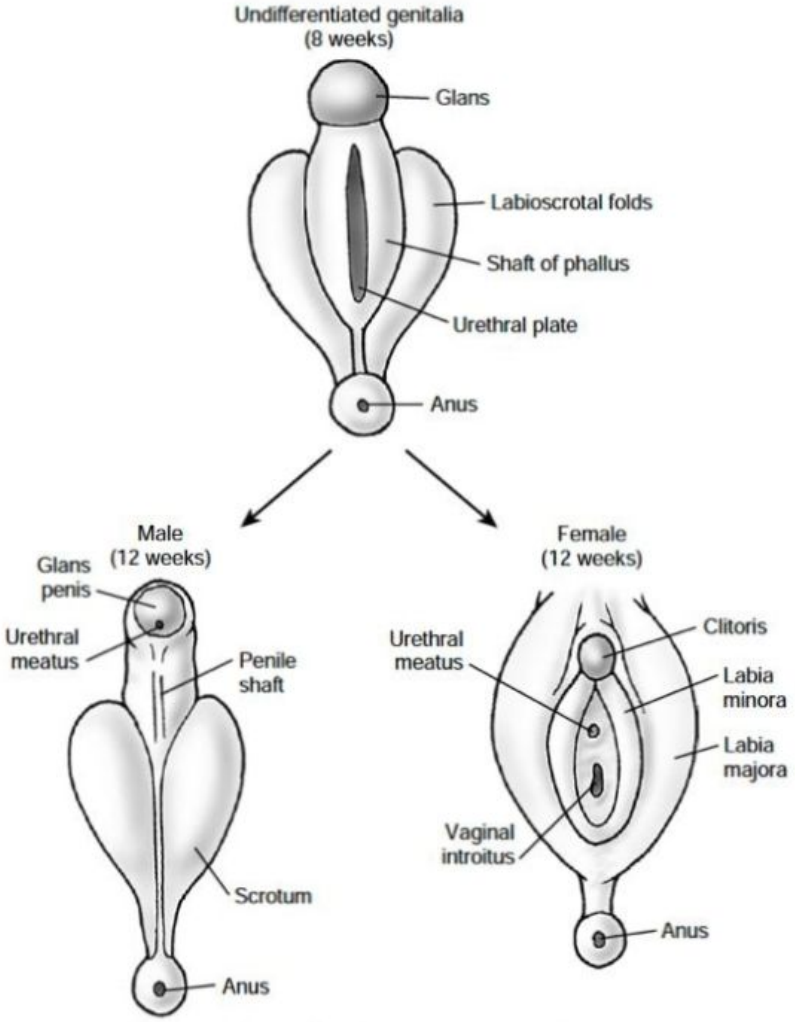

Figure 63-1. Differentiation of the external genitalia.

Classification

The most commonly used classification system was proposed by Allen in 1976.[17] This system categorizes the most common DSD well. However, as our understanding of the less common syndromes evolves, they do not fit as neatly into this paradigm. The five categories are based primarily on gonadal histology:

1. Female pseudohermaphrodite (ovarian tissue only)
2. Male pseudohermaphrodite (testicular tissue only)
3. True hermaphrodite (both ovarian and testicular tissue)
4. Mixed gonadal dysgenesis (testicular tissue and a streak gonad)
5. Pure gonadal dysgenesis (two streak gonads)

More recently, in 2006, a consensus statement was released from the International Consensus Conference on Intersex proposing new nomenclature for these disorders. This new classification system incorporates an evolving understanding of the molecular basis of these disorders and replaces more offensive gender-based labels. For instance, intersex disorders are now called disorders of sexual differentiation. The new terminology for the more familiar previous categories is summarized in Table 63-2. To facilitate this transition, both terms will be used where applicable in this chapter.[18]

Table 63-2 Nomenclature for Disorders of Sexual Differentiation (DSD)

Current	Classic
46,XX DSD	Female pseudohermaphrodite
46,XY DSD	Male pseudohermaphrodite
Ovotesticular DSD	True hermaphrodite
45,XX/46,XY Ovotesticular DSD	Mixed gonadal dysgenesis
46,XX Complete gonadal dysgenesis	Pure gonadal dysgenesis (common form)

46,XX DSD (Female Pseudohermaphrodite)

The majority of neonates with external genital ambiguity fall into this category. All patients have a 46,XX genotype and exclusively ovarian tissue in nonpalpable gonads. Simplistically, the cause of the gender ambiguity is an excess of androgen. More than 95% are due to CAH, with the remainder due to maternal androgen exposure. These patients have a normal female müllerian ductal system with an upper vagina, uterus, and fallopian tubes (see Table 63-1). They also have normal regression of the wolffian ducts. The level of virilization is largely dependent on the timing and magnitude of androgen exposure to the external genitalia. The phenotype can range from mild clitoromegaly to full masculinization.

Virilization in CAH is due to the inability of the adrenal gland to form cortisol. The precursors above the enzymatic defect are shunted into mineralocorticoid or sex-steroid pathways. Also, the end products generally have some, albeit weak, glucocorticoid function. The lack of cortisol for negative feedback inhibition of adrenocorticotropic hormone (ACTH) production by the pituitary leaves this pathway unchecked. Excess androgen is produced and is responsible for the virilization. The corticosteroid synthetic and alternative pathways are diagrammed in Figure 63-2. The most common form of CAH is 21-hydroxylase deficiency (21-OHD), which accounts for more than 90% of CAH.[19] 21-OHD has been mapped to the short arm of chromosome 6. The variable location of the adrenal defect and relative function of the gene results in salt-wasting and non–salt-wasting forms.[20-22] Type 1 (21-OHD) results in virilization but no salt wasting. The gene defect affects only the fasciculata zone of the adrenal, resulting in blocking cortisol production. However, the gene is normally expressed in the glomerulosa zone with preservation of mineralocorticoid production. In type 2 (21-OHD), also called the classic type, the gene abnormality affects both zones of the adrenal. Salt wasting results in dehydration or vascular collapse, and hyperkalemia develops because of the block in mineralocorticoid production.

11β-Hydroxylase deficiency (type 3) is a less common cause of CAH. This gene has been mapped to the long arm of chromosome 8. This abnormality results in virilization associated with hypertension. This effect is related to the level of the synthetic block below deoxycorticosterone (DOC). DOC has potent mineralocorticoid function. Its excess results in sodium resorption, fluid overload, hypertension, and hypokalemic acidosis.

Finally, 3β-hydroxylase deficiency (type 4) is a rare form of CAH. It results in severe salt wasting, and survival is rare. It is the only type of CAH to occur in both genders.

Rarely, virilization of the female fetus can be caused by exogenous androgen exposure from the mother. This occurs primarily with the use of progesterone, commonly used as an adjunct to assist with fertility and with in-vitro fertilization. Previously, androgenic compounds also were administered to expectant mothers with a history of repeated spontaneous abortion as a preventive measure.

Endogenous androgen exposure due to virilizing maternal ovarian tumors also has been reported as a cause of 46,XX DSD.[23] Fortunately, these tumors are usually virilizing to the mother and the fetus is unaffected. Virilizing tumors include arrhenoblastoma, hilar cell tumor, lipoid cell tumor, ovarian stromal cell tumor, luteoma of pregnancy, and Krukenberg's tumor.[24]

Diagnosis

The diagnosis of CAH is based on the previously described clinical and electrolyte abnormalities in addition to elevated 17-hydroxyprogesterone levels. DOC and deoxycortisol levels also aid in determining which enzymatic defect is present. The physical examination is notable for the absence of palpable gonads

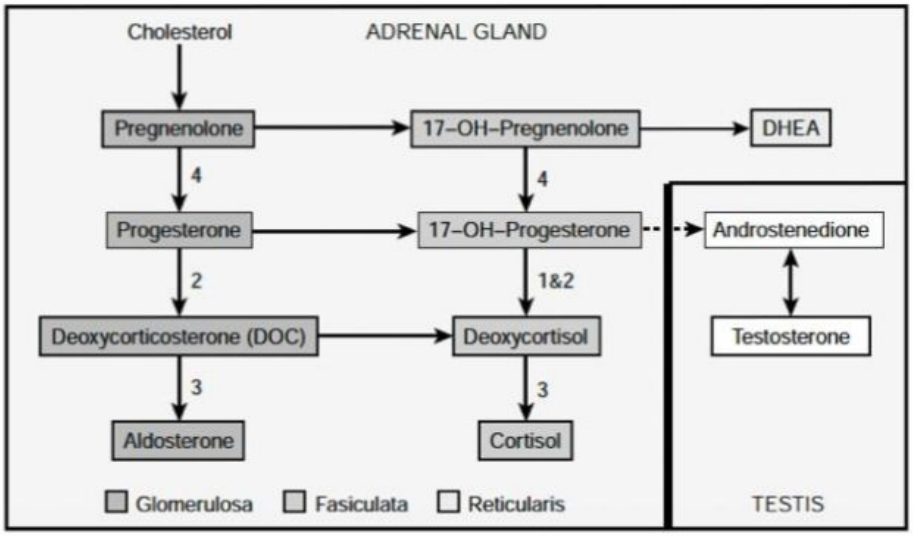

Figure 63-2. Pathways of steroid biosynthesis. The numbers correspond to CAH type and the location of the enzyme defect (see text).

and the presence of a cervix on rectal examination. Also, bronzing of the skin may be noted from excess ACTH cross-reactivity with melanocyte-stimulating hormone receptors. Palpation of a gonad virtually excludes the diagnosis of 46,XX DSD. The genitogram and an ultrasound study mirror these findings, revealing müllerian structures with a variable-length urogenital sinus.

Treatment

Because all forms of CAH are inherited in an autosomal recessive manner, genetic counseling is recommended. Although it is controversial, in families with a history of CAH, maternal treatment with dexamethasone before week 10 of gestation can eliminate or improve the level of fetal virilization and is generally well tolerated.[25] Postnatally, cortisol replacement with hydrocortisone is the mainstay of therapy, with the addition of fluorohydrocortisone if salt wasting is present. Supportive management of fluid and electrolyte abnormalities may be best provided in a neonatal intensive care unit.

With regard to gender identity, the vast majority of patients with CAH identify as female.[26] In this subgroup, gender assignment is uniformly female and is congruous, given a 46,XX karyotype and normal ovaries imparting the potential for fertility. Surgical reconstruction, a feminizing genitoplasty, generally involves three elements: clitoroplasty, monsplasty, and vaginoplasty.

46,XY DSD (Male Pseudohermaphrodite)

This group is the most heterogeneous in the classification system. All patients have a 46,XY genotype and testicular gonadal tissue only. The gonads are sometimes palpable. The condition can be simplistically thought of as a deficit of either production or reception of androgen.

The androgen deficit may result from a defect in synthesis. Several rare enzyme deficiencies have been implicated, including those of 3β-hydroxylase, 17α-hydroxylase, and 20,22-desmolase (cholesterol side-chain cleavage deficiency). All three adrenal enzymes are involved in the steps from cholesterol to androstenedione and testosterone and are associated with severe CAH and often death. 3β-Hydroxylase and 20,22-desmolase deficiencies are associated with cortisol and aldosterone deficits with hyponatremia, hyperkalemia, and metabolic acidosis. In 17α-hydroxylase deficiency, mineralocorticoid production is preserved, resulting in excess salt and water retention, hypertension, and hypokalemia. In the male, the phenotype is variable, ranging from the appearance of a proximal hypospadias with cryptorchidism to that of a phenotypic female with a blind-ending vagina.

Defects in 17,20-desmolase and 17β-hydroxysteroid oxidoreductase act at the testicular level to convert androstenedione to testosterone. Because the adrenal is unaffected, CAH does not occur. The phenotype can be quite variable, but those with complete feminization may escape detection at birth and be reared as female. In the latter disorder, however, progressive virilization is related to excess gonadotropin production at puberty, which may partially compensate for the lack of testosterone synthesis. Phallic growth and the development of male secondary sex characteristics create a conundrum with regard to gender reassignment when the diagnosis is made later in life.[27]

Despite adequate production of androgen, receptor defects can render cells blind to the virilizing effects of the hormone. The phenotype is variable and depends on the degree of insensitivity of the receptor for androgen.

The extreme is normal female external genitalia resulting from complete androgen insensitivity syndrome (CAIS). The incidence of this syndrome is approximately 1 in 40,000. It usually results from a point mutation in the androgen receptor gene, located on the X chromosome.[28,29]

Receptor defects seen in CAIS (also termed *testicular feminization*) result in normal female external genitalia and a blind-ending vagina. Testes are present but may be nonpalpable. MIS production is intact, so no müllerian ductal structures are present. These patients usually are initially seen at puberty with amenorrhea, but may be encountered earlier with the finding of a testis at the time of inguinal hernia repair.

Partial androgen insensitivity is associated with a large spectrum of phenotypic variation (e.g., Gilbert-Dreyfus, Lub's, and Reifenstein's syndromes). It can be a sporadic or inherited condition, and gender assignment and treatment are individualized.[30]

Testosterone is converted to DHT by 5α-reductase, type 2. DHT is a much more potent androgen with regard to virilization of the external genitalia and prostate. The phenotype is ambiguous, but virilization occurs at puberty related to the increased testosterone production and peripheral conversion by nongenital 5α-reductase, type 1. Unfortunately, the virilization is incomplete, and a small phallus and infertility are likely.

Diagnosis

Metabolically, the diagnosis is made similar to that of CAH in the 46,XX DSD patient, noting excess steroid levels above the enzymatic block and elevated levels of ACTH. The physical examination confirms absence of a cervix on rectal examination. Bronzing of the skin may be noted from excess ACTH as well. Palpation of a cryptorchid or descended testis is possible. The genitogram and ultrasound study mirror these findings, revealing no vagina or uterus, but a prominent utricle may be present that lacks a cervical impression at its apex. In CAIS, testosterone levels are elevated postpubertally but the diagnosis in the prepubertal child may require human chorionic gonadotropin (hCG) stimulation and genital skin fibroblast androgen receptor studies. Receptor assays can delineate a quantitative versus qualitative receptor defect. LH levels are elevated, related to the loss of testosterone feedback

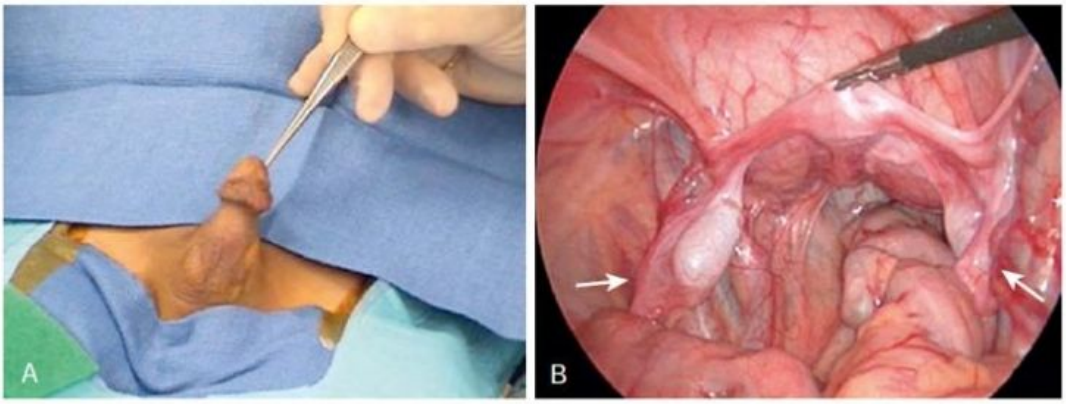

Figure 63-3. A 2-year-old boy presented with nonpalpable testes. A karyotype showed XY. **A,** External genitalia were male. **B,** Laparoscopy revealed bilateral gonads that were testes on longitudinal biopsy. Müllerian structures (*arrows*) were also seen. Note the rudimentary uterus (being held by the grasping forceps). This patient had abnormal MIS-receptor function.

inhibition, which requires normal receptor hormone interaction. 5α-Reductase deficiency is confirmed by an elevated testosterone-to-DHT ratio and an abnormal 5α-reductase type 2 gene.[31]

Treatment

In CAIS, the gender assignment is always female. CAIS patients who are assigned as female in infancy later identify themselves as female.[32] Because the androgen receptor defect is ubiquitous, virilization of the brain does not occur. Orchiectomy is required, given the low but present risk of malignant degeneration, but this is often deferred until after puberty.[33] The testis synthesizes estradiol, facilitating feminine development at puberty. Orchiectomy before puberty necessitates hormone replacement for normal pubertal development.

Gender assignment in partial androgen insensitivity syndrome (PAIS) is largely based on the response of the external genitalia to exogenous testosterone. A significant virilization response argues for the male gender. If there is no response, the female gender is favored. This subgroup is the most variable and has the least consensus with regard to gender assignment. There are reports of gender reassignment at puberty.[34,35] Dissatisfaction with the gender of rearing occurs in approximately 25% of PAIS patients, whether raised male or female.[36] In 5α-reductase deficiency syndrome, the brain is normally virilized and these individuals identify with the male gender. Thus, male gender assignment is recommended.[37]

Müllerian Inhibitory Substance Deficiency

MIS is produced by the Sertoli cells in the testis and causes regression of the müllerian ductal structures. In this rare syndrome of abnormal MIS production or MIS-receptor abnormality, wolffian ductal development is unimpaired but the müllerian ducts also persist. Because the infant has a normal male phenotype, this syndrome is rarely encountered in the neonatal period. The most common presentation to the pediatric surgeon is that of finding a fallopian tube adjacent to an undescended testis in the hernia sac at the time of orchiopexy (hernia uterine inguinale).[38]

If this scenario is encountered, a biopsy of the gonad should be performed, the hernia repaired, and all structures left intact until completion of a full evaluation with karyotype and MIS levels. Apparent males can also present with bilateral nonpalpable testes, and müllerian structures are found at laparoscopy (Fig. 63-3). Abnormal MIS-receptor gene assays also can be helpful for verifying the diagnosis in those with a normal MIS level. Subsequent management is primarily orchiopexy. This, however, may be extremely difficult because the vas deferens can be closely adherent to the fallopian tube or uterus. Excision of discordant ductal structures may be attempted, but, given the relatively low risk associated with leaving these structures, the risk of damage to the vas during this dissection likely outweighs the benefit of removal. Despite normal testosterone levels, impaired spermatogenesis is often the case.[39-41]

Leydig Cell Abnormalities

Because the Leydig cell is responsible for testosterone production in the testes, impaired testosterone production can also manifest from Leydig cell hypoplasia, agenesis, or abnormal Leydig cell gonadotropin receptors. These disorders are rare. Although the karyotype is 46,XY, the phenotype tends to be female, with a blind-ending vaginal pouch and absence of internal müllerian structures. These patients usually are seen initially in the pubertal period with amenorrhea and, therefore, are reared as female. Management is similar to that for CAIS, with orchiectomy and estrogen replacement.[42,43]

Ovotesticular DSD (True Hermaphrodite)

Ovotesticular DSD exists when both ovarian and testicular tissue are present. The gonadal configuration also can be quite variable, with the ovary/ovotestis

combination being most common in the United States. Ovary and testis, bilateral ovotestes, and testis/ovotestis combinations also occur. Ovotestes are usually polar with an ovary at one end and a testis at the other, but the distribution can be longitudinal, requiring deep longitudinal biopsy to sample the gonad adequately. Because of the paracrine effect of the gonad, the ipsilateral internal duct structures correlate with the type of gonad present. Ovotestes are associated with a variable duct structure, but usually fallopian tubes prevail. A decisively müllerian or wolffian duct structure is usually present rather than an ipsilateral combination.[44]

Ovotesticular DSD can be associated with a variety of karyotypes, with 46,XX being the most common. In the United States, the majority with this karyotype are African American, but different chromosomal content has been correlated with different races. It is thought that a translocation of the *SRY* gene or associated genes to an X chromosome or autosome explains the development of testicular tissue in the 46,XX karyotype. It is more difficult to explain ovarian tissue in a patient with a 46,XY karyotype. Likely, key genes to the ovarian development are present, but undetected to complement the normal X chromosomal content. An unappreciated mosaicism could also have occurred.

The phenotype covers the entire spectrum, with ambiguity and asymmetry the rule, but with a tendency toward masculinization. Although it is unusual for ovaries to be found in the labioscrotum, testes and ovotestes are often found descended. Fertility has been described in those raised as female, but testicular fibrosis makes this unlikely in those raised as male.[29,45]

Diagnosis

The diagnosis of ovotesticular DSD is suggested by a mosaic karyotype or ductal structures, but is confirmed by the presence of ovarian and testicular tissue by biopsy.

Treatment

Gender assignment in ovotesticular DSD is quite variable and should be based on the functional potential of the phenotype. In either case, the discordant gonads should be removed early. Retained testicular tissue will cause virilization in the female. In males, the testicular tissue is preserved and orchiopexy is performed. A 1% to 10% incidence of testicular tumor development is found in males, predominantly gonadoblastomas and dysgerminomas, so long-term surveillance is needed.[46] Hypospadias repair also is required in the male, and feminizing genitoplasty is performed in the female. Males tend to require hormonal replacement because of the progressive testicular fibrosis, but females usually do not. Fertility is possible in those raised as female. Females should, however, be screened for testosterone levels, which can signal inadequate resection of testicular tissue.[47]

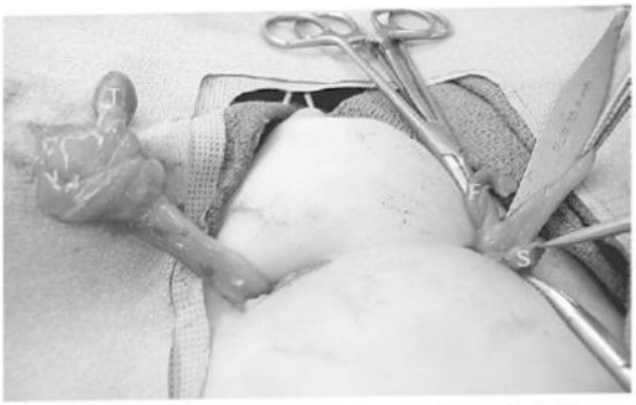

Figure 63-4. Mixed gonadal dysgenesis. The left testis was descended, and the right streak gonad was intra-abdominal. T, testis; F, fallopian tube; S, streak gonad. (Photo taken from head of table.)

Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis (MGD) is the second most common form of neonatal ambiguous genitalia. The patient will have a testis on one side and a streak gonad on the other, characterized by microscopically normal ovarian stroma without oocytes (Fig. 63-4). The internal duct structure mirrors the ipsilateral gonad, with the streak associated with a fallopian tube and uterus resulting from the lack of MIS. The karyotype is generally a mosaic of 45,XO/46,XY, and the stigmata of Turner's syndrome are variably present. The phenotype is ambiguous, but masculinized, and the testis may be descended but more commonly is not.[48]

The risk of gonadal tumor development, usually gonadoblastoma, is as high as 20%, and tumors can develop in either the testis or streak gonad.[49] An increased risk of Wilms' tumor also is present in MGD. The Denys-Drash syndrome occurs in approximately 5% of patients with MGD and is classically described as ambiguous genitalia, Wilms' tumor, and glomerulopathy, which is often seen with hypertension.[50]

Diagnosis

The diagnosis is suggested by the physical stigmata of Turner's syndrome on examination (webbed neck, shield chest) and 45,XO/46,XY karyotype. The finding of a testis and streak gonad, however, confirms the diagnosis.

Treatment

The majority of patients with MGD have been raised as female because of the short stature conferred by Turner's syndrome and the malignant risk of the retained testis. Females undergo early gonadectomy and feminizing genitoplasty. Males require early excision of the streak gonad, orchiopexy or orchiectomy, and hypospadias repair. Infertility is the rule despite adequate testicular endocrine function. Because of the increasing concern regarding testosterone imprinting on the brain, more masculinized patients are being raised as

male. If individuals are raised as male, close surveillance of the testis is necessary, unless elective orchiectomy and hormone replacement are chosen. Testicular biopsy at the time of puberty to exclude dysgenetic elements is generally recommended.[46] If carcinoma in situ is identified, low-dose radiation therapy is curative.

Pure Gonadal Dysgenesis

Pure gonadal dysgenesis (PGD) is characterized by streak gonads bilaterally. The external phenotype and internal duct structures are female. These patients generally are seen at puberty with primary amenorrhea. The chromosomal makeup is classically 46,XX. PGD is an autosomally recessive trait, so genetic counseling is warranted. This implies that the condition can be caused by abnormalities in the X chromosome or supporting autosomal genes involved in gender differentiation. The gonads do not carry risk of malignant degeneration.

Other conditions are also closely related to bilateral streak gonads. The chromosomal makeup is quite variable and can be 46,XY (XY sex reversal, Swyer's syndrome, or male Turner's syndrome), 45,XO, or a mosaic. Variants with a Y chromosome differ in that they carry a high rate of malignancy in the retained streak gonads. The phenotype is as described earlier, but these patients may be first seen in infancy with gonadoblastomas or dysgerminomas, or with germ cell tumors that become more common in adolescence. The stigmata of Turner's syndrome are often present. Multiple chromosomal deletions and mutations have been described causing this syndrome.

Diagnosis

The finding of a female external phenotype and an internal duct structure with bilateral streak gonads confirms the diagnosis. Follicle-stimulating hormone and LH levels are generally elevated, and estrogen and testosterone levels are decreased. The diagnosis may be suggested by the physical stigmata of Turner's syndrome on examination (e.g., webbed neck, shield chest).

Treatment

With the presence of a Y chromosome, gonadectomy should be performed, given the high incidence of malignancy. In classic 46,XX PGD, the gonads can be left in situ because there is no malignant potential. In either case, hormonal replacement at puberty is required because the streak gonads provide no endocrine function.

Other Syndromes of Aberrant Sexual Differentiation

Several syndromes worth mentioning do not neatly fit into the described classification systems.

Vanishing testis syndrome is characterized by a 46,XY karyotype but absent testes bilaterally. This generally results in virilization to the point of normal external genitalia and internal duct structure but absent testes. The testes were thought to have produced androgen at some point, resulting in this masculinization, but subsequently vanished related to torsion or regression. Patients are generally raised as boys, and hormonal supplementation at puberty is required.[51]

Klinefelter's syndrome is characterized by a male karyotype containing two or more X chromosomes (47,XXY; 48,XXXY; etc.). Although phenotypically male prepubertally, these patients acquire abnormal male secondary sexual characteristics (tall stature with disproportionately long legs, sparse facial hair, decreased muscle mass, and a feminine fat distribution) and infertility. The testes are small and hard, with decreased androgen production and elevated estradiol levels related to primary hypergonadotropic hypogonadism. Gynecomastia often occurs with an increased risk of breast cancer.[52] Fertility has been reported but requires assisted means, such as intracytoplasmic sperm injection.[53]

46,XX Testicular DSD (XX sex reversal) is characterized by a male phenotype with a 46,XX karyotype. Most commonly this occurs from translocation of Y chromosomal material to the X chromosome, but it also can occur from mutation of the X chromosome or from mosaicism. The phenotype and management are similar to those of Klinefelter's syndrome, with the exception of shorter stature.[54]

Mayer-Rokitansky-Küster-Hauser syndrome is characterized by a 46,XX karyotype with normal female external genitalia but a short, blind-ending vagina. Normal ovaries and fallopian tubes are present, but the uterus is generally rudimentary. Patients are seen initially with primary amenorrhea but may have cyclical pain related to functioning endometrium. Treatment is geared toward vaginal reconstruction to allow menses or intercourse, or both.[55]

EVALUATION OF THE NEWBORN WITH AMBIGUOUS GENITALIA

The diagnosis of ambiguous genitalia is extremely disconcerting to the family and should be addressed as a medical emergency. Usually, genital ambiguity is obvious, but the finding of any degree of hypospadias in association with any undescended testis or of a normal penis with bilateral nonpalpable testes merits an intersex evaluation. In this population, a high rate of intersex conditions is found despite the absence of classic ambiguity.[56] Table 63-3 indicates other abnormal

Table 63-3 Abnormal Physical Examination Findings for Disorders of Sexual Differentiation

Apparent Female	Unsure	Apparent Male
Clitoral hypertrophy	Ambiguous	Impalpable testes
Fused labia		Severe hypospadias
Palpable gonad		Hypospadias and cryptorchidism

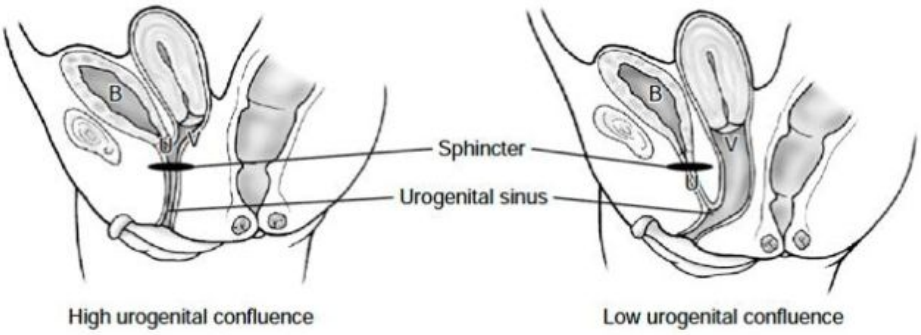

Figure 63-5. High versus low urogenital confluence. B, Bladder; U, urethra; V, vagina.

physical examination findings that warrant consideration for DSD.

The family history may reveal maternal hormone exposure, previous fetal death, or a history of genital ambiguity.

The physical examination should focus on the genitalia. Assessment for palpable gonads is important, because a palpable gonad represents a testis or ovotestis and rules out 46,XX DSD, in which only ovaries are present, or PGD, in which only streak gonads are present. If both gonads are palpable, this generally indicates 46,XY DSD. One palpable gonad is generally associated with MGD or ovotesticular DSD. Phallic stretched length, clitoral size, and the position of the urogenital sinus should be noted. A rectal examination may reveal a palpable uterus. The physical examination should include assessment for the stigmata of Turner's syndrome associated with MGD and PGD. Bronzing of the areola or scrotum can suggest elevated ACTH production in CAH.

The initial metabolic evaluation should include a karyotype or fluorescent in-situ hybridization to identify X and Y chromosomes. 17-OH progesterone levels should be obtained after 3 or 4 days of life, by the time spurious elevations resulting from the stress related to birth have subsided. Electrolyte levels should be monitored closely in the interim to identify salt wasting with CAH. Testosterone and DHT levels are important for evaluating 5α-reductase deficiency. An elevated LH level and a low MIS level suggest testis dysgenesis or absence. ACTH or hCG stimulation tests can be performed but are more controversial.[38]

Early imaging studies include pelvic ultrasonography, which should identify a uterus if one is present. Although a gonad may be seen, ultrasonography is not useful in differentiating a testis, ovotestis, or ovary. A genitogram performed by retrograde contrast injection into the urogenital sinus is helpful in identifying the level of confluence of a vagina and urethra and its relation to the urethral sphincter (Figs. 63-5 and 63-6).

Gonadal biopsy is often required for diagnostic purposes, but the diagnosis of CAH can be made by metabolic evaluation alone. Endoscopy is not usually required for diagnosis, but is essential in characterizing the internal duct structure, level of confluence of the urogenital sinus, and planning for and performing the reconstructive surgical procedures.[29]

At my institution, a gender-assignment team including a pediatric urologist/surgeon, endocrinologist, geneticist, neonatologist, psychologist, and social worker together evaluate any newborn with ambiguous genitalia. This information is synthesized by the team and presented to the parents in a combined care conference. The goals of gender assignment and management should include preservation of sexual function and any reproductive potential with the least number of operations, appropriate gender appearance with a stable gender identity, and psychosocial well-being.[57]

RECONSTRUCTIVE GENITAL SURGICAL PROCEDURES

Controversies and Considerations

For more than 20 years, largely based on the work of John Money and the "John/Joan Case," the overwhelming bias was that gender identity was largely inducible and loosely dependent on chromosomal constitution. The focus was on one of two twin boys who was reassigned to the female gender early in life after a demasculinizing circumcision injury. The child reportedly developed normally from a psychosocial

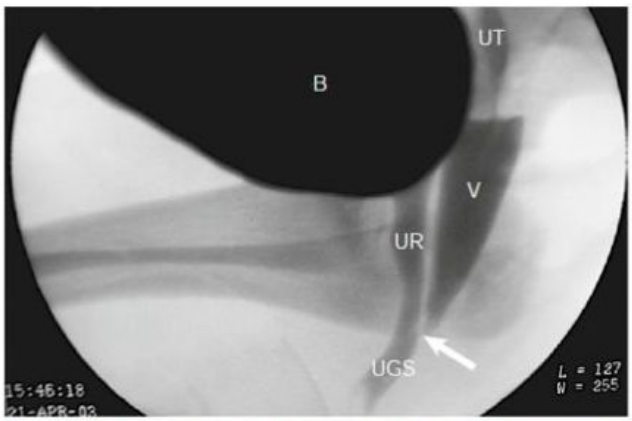

Figure 63-6. Genitogram, lower confluence. *White arrow,* level of the confluence of urethra and vagina to become the urogenital sinus. B, Bladder; UT, uterus; V, vagina; UR, urethra; UGS, urogenital sinus.

standpoint, well adapted to life as a girl.[58] Only with extended follow-up into adulthood was it discovered that the individual converted back to male gender after severe dissatisfaction with a female identity (including attempted suicide).[59] This rattled the fundamental concepts on which gender assignment had been based for decades and brought to the forefront a tremendous controversy regarding the appropriate management of children with ambiguous genitalia and possible gender reassignment.

Because reconstruction is rarely done in response to any life-threatening issues, support groups for individuals with intersex conditions have advocated delaying any reconstruction until the child can express his or her wishes regarding gender assignment.[60] Although this would decrease the likelihood of a mismatch between physical and psychological gender, the period of genital ambiguity could be quite challenging for a child in our society. Despite the controversy, the International Consensus Panel on Intersex stated that, currently, the evidence is insufficient to abandon the practice of early genital reconstruction.[18] However, all these options must be discussed thoroughly with the family before embarking on any reconstructive efforts.

In general, if surgical reconstruction is thought to be appropriate, it is planned in the first 3 to 6 months of life. For feminizing reconstruction, the vaginal tissue is thicker as a result of maternal hormonal influence and the distance from the vagina to perineum is shorter at this age. Because parents have a great degree of anxiety surrounding the gender of their child, earlier repair may help reduce this anxiety and encourage parent/child bonding.[61]

Male Gender Assignment

Reconstructive efforts for the male gender of rearing include orchiopexy or orchiectomy, when appropriate, and hypospadias repair. These techniques are described elsewhere in this text. It bears mentioning, however, that orchiopexy may be extremely difficult because the vas deferens can be closely adherent to müllerian duct remnants, such as a fallopian tube or uterus. A portion of these structures may be left in situ if the risk of damage to the vas deferens or testicular vasculature is significant, but this adherence may severely limit mobility of the testis and preclude orchiopexy.

Methods of total penile reconstruction in cases of aphallia, demasculinizing penile trauma, or female-to-male gender reassignment by using a radial forearm or osteocutaneous fibula flap have been described with some reasonable success.[62,63] These corrective efforts are usually undertaken in adulthood, and their description is beyond the scope of this discussion.

Female Gender Assignment

Feminizing genitoplasty includes three major components: monsplasty, clitoroplasty, and vaginoplasty (Figs. 63-7 and 63-8). The timing of the vaginoplasty depends on the level of confluence of the urogenital sinus. For a low confluence, it is performed in the neonatal period with monsplasty and clitoroplasty. If the confluence is high, this may be approached simultaneously. However, because vaginal dilation is often necessary after repair, this may better be deferred until the patient is peripubertal and more capable and interested in this requirement. Cystoscopy is invaluable for this assessment. We generally introduce a Fogarty balloon catheter in the vagina and a catheter in the urethra and bladder to define the confluence during dissection.

The procedure is initiated by placing a traction suture in the glans, and a dorsolateral circumcising incision is made, leaving a 4- to 5-mm distal preputial cuff, much like is done in a hypospadias repair. The lateral borders of the mucosalized plate are incised, taking this back adjacent to the urogenital sinus. The shaft of the phallus is then degloved of skin superficial to Buck's fascia. Fascial incisions are then made lateral to the neurovascular bundles. A plane is created just beneath Buck's fascia from the level just proximal to the glans back to the pubic symphysis. The mucosalized plate is elevated on the ventrum and preserved

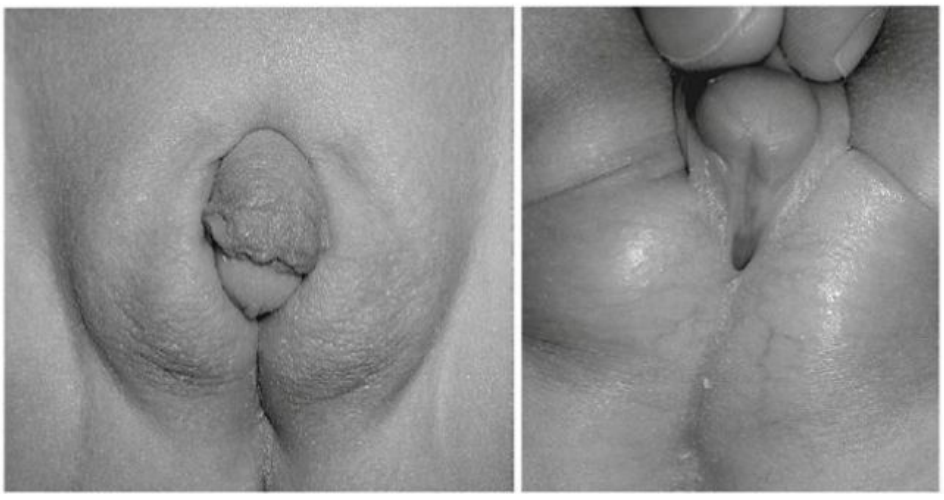

Figure 63-7. Ambiguous genitalia. The patient has congenital adrenal hyperplasia, 21-hydroxylase deficiency.

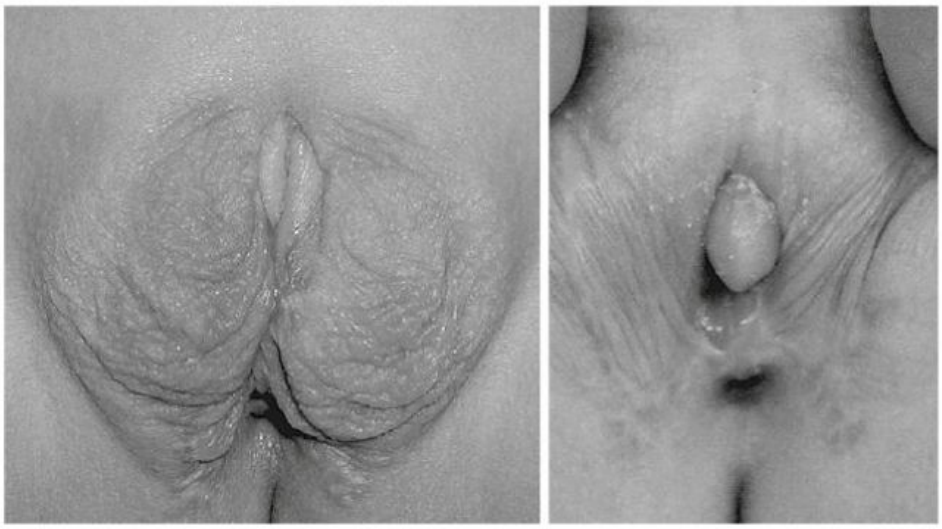

Figure 63-8. Same patient as in Figure 63-7. Appearance of genitalia 6 months after undergoing a feminizing genitoplasty.

to fill naturally the void between the urethral meatus and clitoris. The dorsal pedicles, including the neurovascular bundles, are preserved. The corporeal bodies are suture ligated at their base at the level of the pubic symphysis, and the distal corporeal tissue is excised. An alternative technique preserving the corporeal bodies has been described to maintain the potential for reversibility, but long-term functional outcome is pending.[64]

I do little to reduce the size of the glans clitoris because I believe that even when it is markedly enlarged, it can be recessed and has a quite normal appearance in adulthood. By not trying to reduce the size of the clitoris, nerve injury is limited. However, alteration in sensation is more commonly associated with clitorectomy rather than clitoral reduction.[65] The clitoris is anchored to the corporal stumps to secure its position, being sure not to compromise the dorsal neurovascular pedicle.

A posterior inverted "U"-shaped flap is then made from the level of the ischial tuberosities to just posterior to the urogenital meatus. For a very low confluence, dissection is carried along the posterior aspect of the urogenital sinus to the level of the confluence, the posterior wall is incised until the vaginal introitus is normal in caliber, and the "U"-flap is advanced to complete the posterior vaginal wall (Fig. 63-9). With higher confluences, my colleagues and I have favored total urogenital mobilization.[66-68]

For total urogenital mobilization, the urogenital sinus is incised circumferentially and mobilized as one unit to the level of the confluence (Fig. 63-10). At this point, the vagina can be carefully separated from the urethra under direct vision and the defect in the urethra is closed. The urogenital sinus can then be incised at the dorsal midline and folded back onto itself to make up the anterior vaginal wall. By using local skin flaps for the dorsolateral defects, a lengthy distance can be bridged.

Total urogenital mobilization is attractive in that one can approach even the high urogenital confluence in the neonatal period without vaginal substitution or grafting, but the family must be appropriately cautioned. Although early results are favorable, descent of the bladder neck is counterintuitive when considering our knowledge of adult female stress incontinence and long-term continence may be an issue. To complete the monsplasty, the dorsal phallic shaft skin is incised vertically, a preputial hood is formed for the clitoris, and the majority of this tissue is used to construct the labia minor with "V"-shaped advancement flaps (Fig. 63-11).

Other techniques for the high urogenital sinus include a posterior approach dividing the rectum and

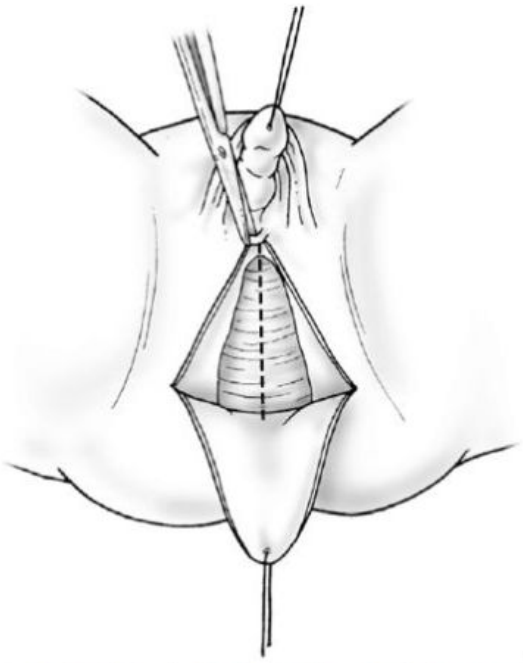

Figure 63-9. Vaginal cutback procedure for the low urogenital confluence.

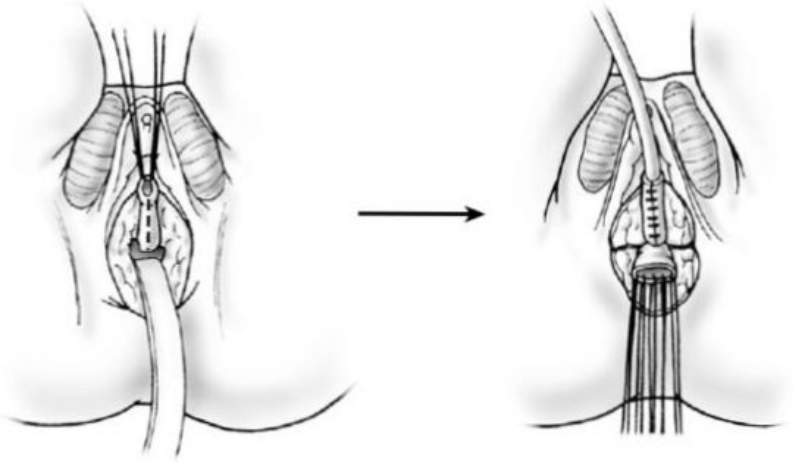

Figure 63-10. Total urogenital mobilization. The urogenital sinus is mobilized as a unit, bringing the confluence toward the perineum. Once visualized, the vagina is then detached and the urethral defect is closed.

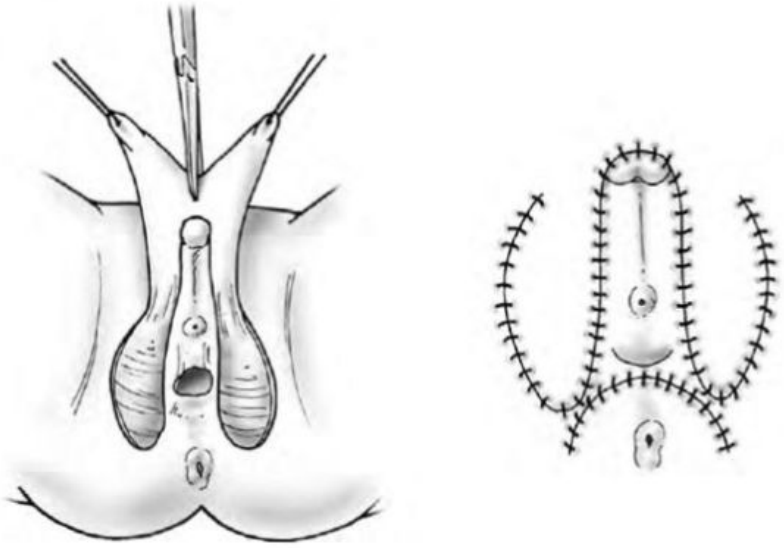

Figure 63-11. Mons plasty. Dorsal shaft skin is degloved from the phallus and incised. These flaps are then advanced to become the labia minora. (Shown before and after excision of the corporeal tissues and clitoropexy.)

an anterior transvesical approach.[69,70] These methods have not been used extensively at my institution.

In some patients with a high urogenital confluence, I have delayed vaginal reconstruction until the peripubertal period, just before menarche. The techniques described are still used, but in some patients, especially those who are obese, these methods are insufficient. I have favored vaginal substitution with a colonic segment, but ileal substitutions and split-thickness skin grafts also have been advocated. The benefit of vascularized bowel substitution is less vaginal stenosis and the natural formation of lubricating mucus, but this may require wearing a pad if there is excessive mucus production. Colonic segments appear to have a lower rate of stenosis than do ileal segments.[71] Conversely, skin grafts have a tendency toward long-term stenosis and may require frequent dilation and revision, but long-term satisfaction also has been described.[72] The barrier function to sexually transmitted diseases is likely superior with skin grafts when compared with intestine.[73]

In cases of vaginal agenesis (e.g., Mayer-Rokitansky-Küster-Hauser syndrome), the substitution techniques described are often used. However, if a rudimentary vagina or depression exists, sequential dilation with the technique described by Frank and modified to a dilating seat by Ingram may be successful.[74,75]