CHAPTER 1

General Considerations

Chapter Outline

Introduction

Hypospadias is a common congenital anomaly of the penis. The term "hypospadias" refers to a urinary opening situated on the undersurface of the penis, instead of the tip of the penis. This abnormality of the urethral opening is usually associated with other abnormalities like penile curvature/bend (chordee), foreskin abnormalities, and poor tissue development in the penis, and may be associated with a small-sized penis and anomalies in the testis. The extent to which these anomalies are present determines the severity of the condition, which in turn determines the plan of surgical treatment and the outcome.

Embryology

The complete embryology of the development of external genitalia is beyond the scope of this book. Only a brief insight into the possible embryology of hypospadias formation is presented here.

Development of External Genitalia

The external genitalia of the developing fetus are initially indifferent and can develop into either the male or female phenotype. Unless proper

androgenic stimulation occurs between the 9th and 12th weeks of gestation, these primordia of the external genitalia would become a female phenotype. When appropriate hormone stimulation occurs at the appropriate gestation, it causes the genital tubercle to elongate, causes fusion of the urethral folds, and tubularizes the urethral groove beginning proximally and continuing to the level of the glans. It is generally believed that the spongy urethra and the glanular urethra have different embryological origins. The epithelium of most of the male urethra is derived from the endoderm of the urogenital sinus. The distal part of the urethra in the glans penis is derived from a solid cord of ectodermal cells that grows from the tip of the glans and joins the rest of the spongy urethra. Thus, the epithelium of the terminal part of the urethra is derived from the surface ectoderm. The connective tissue and smooth muscle of the urethra are derived from splanchnic mesenchyme.

The currently accepted theories are fusion theory for the development of the spongy urethra and ectodermal ingrowth or endodermal transformation theories for the development of the glanular urethra. Although Hadidi et al recently questioned these concepts, they still remain the most widely accepted theories for the development of the human urethra. Masculinization of the indifferent external genitalia is induced by dihydrotestosterone that is produced peripherally by 5α-reductase conversion of testosterone from the testicular Leydig cells. As the primordial phallus enlarges and elongates to become the penis, the urogenital folds form the lateral walls of the urethral groove on the ventral surface of the penis. This groove is lined by a proliferation of endodermal cells, the urethral plate, which extends from the phallic portion of the urogenital sinus. The urethral folds fuse with each other along the ventral surface of the penis to form the spongy urethra. The surface ectoderm fuses in the median plane of the penis, forming the penile raphe and enclosing the spongy urethra within the penis. The exact formation of the human urethra within the glans penis is unclear, but examination of human embryos suggests that the solid glans plate canalizes and joins the developing penile urethra to form the glans urethra and external

urethral meatus. At the tip of the glans penis, an ectodermal ingrowth forms a cellular ectodermal cord that extends toward the root of the penis to meet the spongy urethra. This cord canalizes and joins the previously formed spongy urethra. This juncture completes the terminal part of the urethra and moves the external urethral orifice to the tip of the glans penis. During the 12th week, a circular ingrowth of ectoderm occurs at the periphery of the glans penis. When this ingrowth breaks down, it forms the prepuce (foreskin). The corpora cavernosa and corpus spongiosum develop from mesenchyme in the phallus. The labioscrotal swellings grow toward each other and fuse to form the scrotum. The line of fusion of these folds is clearly visible as the scrotal raphe.

To summarize, the genital tubercle develops during the fourth week of gestation as the precursor of the phallus. Endodermal cells migrate from the cloaca along its ventral midline to form the urethral plate and on either side proliferating mesenchyme form the urogenital folds. From the 9th to the 12th week, androgenic stimulation causes phallic development. Elongation of genital tubercle occurs, and the urogenital folds migrate to the midline and fuse enclosing the urethral groove. This process moves proximal to distal creating the urethra. As the plate tubularizes, mesoderm within the urethral folds differentiates into the corpus spongiosum, which then fuses distally to the glans. Mesoderm also forms the corpora cavernosa. Development of the penis proceeds at different rates along the ventral and dorsal surfaces resulting in temporary ventral curvature. Similarly, the dorsal prepuce extends beyond the glans before the ventral aspect, which follows closure of the urethral groove. Midline fusion of the ventral prepuce results in the frenulum.

There have been efforts to develop an animal model similar to human external genitalia development. The most important step in sex differentiation of external genitalia is urethral tubularization in males. In humans, this process is described as double zipper model in males. This distal-opening-proximal-closing process of tubular urethra formation has never been clearly shown in any published animal models.

Recently, some authors reported that urethral groove formation and urethral tube closure process of guinea pigs are more similar to humans, making this a more suitable model to study closure of the tubular urethra. Further, in their guinea pig model, hypospadias could be induced by prenatal anti-AR bicalutamide in males, and additional androgen methyltestosterone in utero exposure resulted in tubular urethra formation in females. Thus, the use of this animal model may allow further study of cellular and molecular mechanisms involved in the tubular urethra formation and the evaluation of the pathophysiological processes of hypospadias.

Embryological Basis of Hypospadias

Hypospadias appears to represent an arrest of penile development, more specifically an arrest of urethral formation. The formation of glanular hypospadias may be influenced by multiple factors, but its direct cause is probably defective canalization of the distal glans plate. The arrest or nonfusion of urethral folds causes other (more severe) types of hypospadias. Thus, the urethral opening may be found anywhere along the ventral midline from the perineum to the glans depending on the time at which fusion of the urethral folds was arrested. The nontubularized, flat residual tissue in the midline represents the urethral plate, extending from the meatus to the glans. In severe forms of hypospadias (penoscrotal, scrotal, and perineal forms), apart for an arrest of fusion of the urethral folds, there is also an arrest of fusion of labioscrotal folds. If the labioscrotal folds fuse partially, scrotal hypospadias may result; when the labioscrotal folds do not fuse at all, a completely bifid scrotum with perineal hypospadias will result (**Fig. 1.1**).

Along with these changes, there is arrested or poor development of ventral tissues of the penis to a varying degree. Thus, these defects can be seen as a distal urethral plate of variable quality, open glans wings (split glans penis open like a book, instead of being closed like a cone);

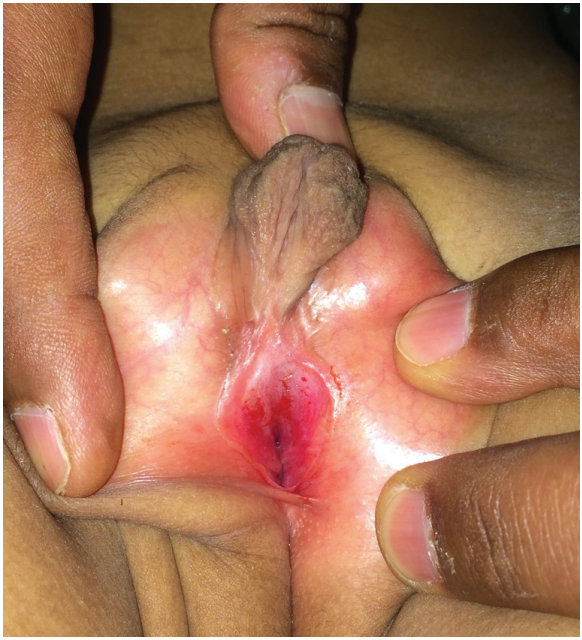

Fig. 1.1 Perineal hypospadias with completely bifid scrotum. In this extreme case, the blind-ending vagina can also be seen opening onto the perineum behind the urethral opening. Both the testes can be seen in the labioscrotal folds. Karyotype was 46XY.

an abnormal, splayed corpus spongiosum; and an absent ventral prepuce (except in some special cases). Most often, apart from the abnormalities discussed above, an abnormal ventral or downward bending/angulation of the penis, called "chordee" may be present.

Etiology of Hypospadias

The etiology of hypospadias has been a subject of much speculation and research, but the exact cause is still unknown. The various causes that have been proposed are genetic, endocrine (hormone) related issues, or environmental agents.

Genetic

In most boys, particularly those with mild or moderate defects (distal or midshaft forms), genetic factors may not play a major role. However, genetic factors (with multifactorial inheritance) may play a role in severe forms of hypospadias, with a 10 to 20% risk of recurrence in the siblings. Heritability of hypospadias is definitely high; there is no doubt that genetic abnormalities are involved, and many different candidate genes and polymorphisms have been suggested for hypospadias. Although some associations with hypospadias were found, none of these associations have been replicated consistently in all studies. Each mutation may explain selective pathogenic factors in only a few percent of hypospadias cases. It is most likely that the majority of isolated hypospadias cases are a result of several additive low-grade genetic risk factors.

Endocrine

The role of maternal endocrine factors leading to hypospadias in the baby has been investigated. Some studies have found a small but significant increase in the incidence of hypospadias in the offspring of women receiving estrogen treatment in pregnancy. Defects in testosterone synthesis have been found in some boys with hypospadias, but the findings have not been consistent. However, a subgroup of boys with severe hypospadias may have 5α-reductase enzyme deficiency, which may present as 45XY disorder of sexual differentiation (DSD). Mutations that reduce or disable this enzyme have little consequence in females, but in males the resulting loss of dihydrotestosterone results in severe penoscrotal hypospadias and genitalia that seem to be female at birth. These individuals have normal testes located in the inguinal region or inside the labioscrotal folds. The testes produce antimullerian hormone (AMH) and testosterone at appropriate times, so paramesonephric duct derivatives are absent, and the mesonephric ducts differentiate into vasa deferentia. In 46XY DSDs of this type, the sudden rise of testosterone at puberty may

cause dramatic differentiation of the external genitalia and accessory glands into typically male structures. The urethral folds and labioscrotal swellings may fuse completely, and the genital tubercle may differentiate into a penis. The normal testosterone levels during fetal life and after puberty are thought to result in normal male differentiation of the brain and, hence, a sense of male gender identity. Thus, these children may present as adolescents for hypospadias repair.

Another endocrine-related cause of hypospadias is androgen insensitivity syndrome (AIS), where androgen receptors are reduced or absent. The male fetus may have normal or high levels of male steroid hormones, but the target tissues do not respond, and development proceeds as though androgens were absent. AIS may be partial or complete: Partial AIS presents with severe hypospadias, small phallus, penoscrotal transposition, and bifid scrotum with usually descended gonads (testes). These children are usually reared as males and come for hypospadias repair. Because of the small phallus, they may require preoperative testosterone injections; however, because of androgen resistance, they require higher doses of hormones. As in cases of primary testosterone deficiency, testes are present and AMH is produced, so the paramesonephric ducts regress, although a blind-ending vagina (enlarged prostatic utricle) may form; these cases, in particular, may pose difficulty in catheterization during hypospadias repair. The complete form of AIS presents a phenotypic female and is referred to as testicular feminization syndrome.

Environmental

Apart from genetic and hormonal defects, a variety of dietary (soya, nonorganic diet) and environmental agents (oral contraceptive pills, pesticides, detergent agents, compounds used in the manufacture of plastics, and some medications) have been shown to have mild hormonal activity and have been implicated in the causation of hypospadias. Most of these agents have only weak estrogen activity and usually occur in low concentrations; hence, at low concentrations they are unlikely to exert

a significant direct estrogenic effect on the fetus. However, even low concentrations of these agents may interfere with androgen biosynthesis and block androgen receptor expression. Thus, the role of these environmental agents in hypospadias causation may be mediated via disruption of androgen pathways rather than a direct estrogenic hormonal effect on the fetus. Although strong evidence supports an association of valproic acid, which has gonadotropin-releasing hormone-agonist properties and thus results in antiandrogenic effects, and in utero exposure of mothers of male babies to diethylstilbestrol (DES) with hypospadias, many other medications including iron, loperamide, antiretroviral agents, nystatin, loratadine, and corticosteroids, along with fertility treatments and maternal cocaine usage, require further investigation to determine whether these are connected with hypospadias development.

Some investigators have found a 50% higher incidence of hypospadias in the offspring of women aged 35 years or older than in the offspring of mothers aged younger than 20 years. In addition, low birth weight is associated with an increased risk, which is independent of gestational age, and some (but not all) studies have reported a significantly greater risk of hypospadias after in vitro fertilization. Further, maternal factors such as obesity, advanced maternal age, age at menarche, parity, diet, ethnicity, and underlying conditions like diabetes and thyroid disease need to be confirmed by further research in regard to their association with hypospadias. Endocrine disruptors also remain controversial as to their relationship with hypospadias, necessitating additional investigation.

Factors most likely associated with hypospadias in most studies are placental insufficiency, low birth weight/small for gestational age, maternal hypertension and preeclampsia, maternal intrauterine DES exposure, and maternal use of antiepileptics. The consistent association of hypospadias with intrauterine growth retardation, low birth weight, maternal hypertension, and preeclampsia suggests that placental insufficiency is a major risk factor for hypospadias, possibly through inadequate provision of human chorionic gonadotrophin to stimulate fetal androgen production. Male infants conceived with the aid of intracytoplasmic

sperm injection may have an increased risk of being born with hypospadias. A study from China found that the risk of hypospadias was higher for children of mothers older than 35 and younger than 18 years of age and in mothers who had consumed alcohol, used drugs, and had an infection during pregnancy. The risk of hypospadias was also higher when mothers and fathers were engaged in agriculture.

In addition to all this information, a recent study has identified an increased risk of neurodevelopmental disorders in patients with hypospadias, as well as an increased risk for autism spectrum disorders in their brothers, suggesting a common familial (genetic and/or environmental) liability.

To summarize, current available evidence suggests that hypospadias is a complex disorder because both genetic and environmental contributors are involved. Hypothetically, a genetic predisposition in combination with placental insufficiency may indicate a strong two-hit risk factor model necessary for a hypospadias phenotype. It has also been hypothesized that in most cases, hypospadias develops because of gene–environment interactions, and both these must coexist for hypospadias formation. Furthermore, it has been shown that interactions between genetic and environmental factors may help to explain nonreplication in genetic studies of hypospadias.

Incidence

Although highly variable, the incidence of hypospadias is about 0.3 to 0.6% boys (1 in 150 to 1 in 300 boys). There is some evidence that the incidence of hypospadias is increasing, presumably due to dietary and environmental agents. One study from Sweden demonstrated an increased incidence of hypospadias diagnoses in Sweden from 1990 to 1999 that was not attributable to previously known risk factors. This increase included both mild and severe types of hypospadias, suggesting that this reflected an actual increase in the incidence of hypospadias. In India, it

is roughly estimated that about 70,000 to 75,000 boys may be born with hypospadias every year.

Severity and Classification

The severity of hypospadias is traditionally determined by the position of the urethral meatus and the extent of ventral penile angulation (chordee). However, the location of the urethral opening may be misleading in some cases, when a length of distal urethra may be thin without corpus spongiosum cover. A more accurate estimate of severity may be used to identify the level of division of corpus spongiosum. Similarly, after correction of chordee, the urethral opening may be moved downward. Many a time, these variations can only be identified during the surgery by assessing the quality of tissues. Thus, preoperative assessment in the clinic may underestimate the true severity of the hypospadias, and this has to be kept in mind when counseling the parents in the clinic. An important practical lesson is not to decide on the technique of operation until the true severity of the defect and the quality of tissues available for reconstruction are correctly assessed during surgery.

Although there are many ways to classify hypospadias, a simple way is to classify it as distal, mid, and proximal. Another practical method used to classify hypospadias is based on the presence and severity of chordee. The practical implication of such a classification is obvious; the cases with no chordee or only mild chordee may be mostly corrected in a single operation, whereas those cases with severe chordee usually require two operations to correct them.

According to Mouriquand, a more practical method is to classify hypospadias on the basis of the level of division of corpus spongiosum. The hypospadiac penis has hypoplastic ventral tissues distal to the division of the corpus spongiosum. This is seen as a ventral triangular defect whose summit is the division of the corpus spongiosum, whose sides are represented by the two pillars of atretic spongiosum, and whose base is

the glans itself. This triangle in some cases contains a segment of variable length of atretic urethra (not surrounded by any spongiosum) which starts where the corpus spongiosum divides. Therefore, it is possible to distinguish two main types of hypospadias: one with a distal division of the corpus spongiosum with little or no chordee and another with a proximal division of the corpus spongiosum with a marked degree of hypoplasia of the tissues of the ventral penis, with a significant degree of chordee. Besides these two main types, there is also hypospadias for which several procedures have failed (hypospadias cripple). In author's experience, the identification of the level of division of corpus spongiosum is a much better indicator of the severity of hypospadias than the location of urethral meatus (**Fig. 1.2**).

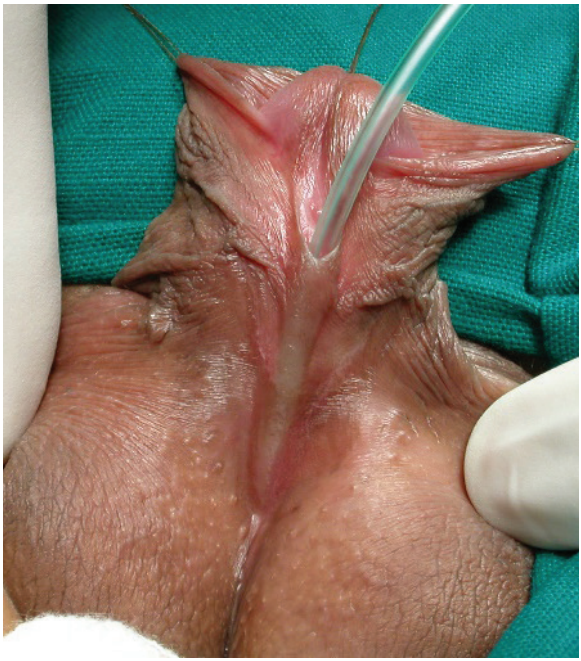

Fig. 1.2 Hypospadias with apparently midpenile opening but severely hypoplastic urethra (lacking spongiosum cover) till the perineum.

Presentation and Initial Evaluation

Hypospadias is usually recognized during initial physical examination of a newborn baby. Typically, the abnormal prepuce (dorsal hood with absent ventral foreskin) gives a clue to the anomaly; further clinical examination often finds the glans tilted downward and the penile raphe displaced from the midline. The meatus will be seen to be on the undersurface of the penis (**Fig. 1.3**).

The meatus may appear small in size (the so-called "pinhole" meatus), but surprisingly, even such small meatus is quite pliable and does not usually cause significant obstruction to urine flow. Ventral curvature of the penile shaft may be noted during erection.

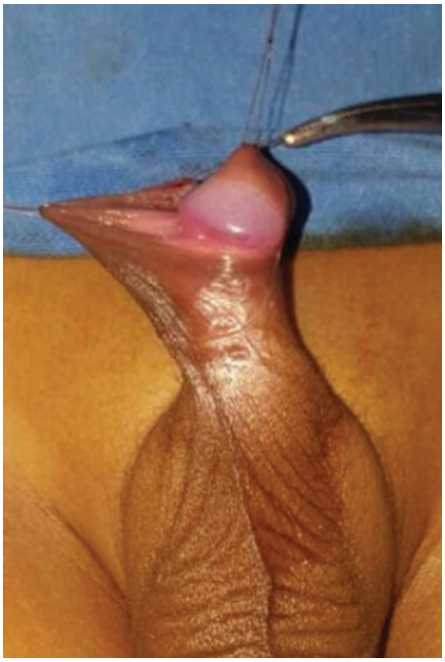

Fig. 1.3 Hypospadias with penile torsion. Note that the torsion is to the left, while the midline raphe is deviated to the right side.

These characteristics, the dorsal hood, altered glans shape, and penile curvature, also can now be identified prenatally by fetal ultrasonography. Observation of micturition from the misplaced meatus confirms the diagnosis. However, the law in India forbids the reporting of external genitalia of the fetus and fetal sex determination; hence, the diagnosis of hypospadias is always made after birth.

When a baby with hypospadias is seen, it is important to examine the testes also. In case of hypospadias with undescended testis (UDT) or severe hypospadias, it may be necessary to obtain a karyotype for associated DSD. It is not generally necessary to get an ultrasound of the kidneys in all children with hypospadias because the association of upper urinary tract abnormalities is low. However, in severe hypospadias, in a child with history of urinary infection or a child with multiple anomalies, an ultrasound examination of the kidneys and bladder may be obtained.

Associated Anomalies

Undescended Testis

Since both hypospadias and UDT may result from male hormone deficiencies, it is possible for the two conditions to coexist in the same child. Some studies report that approximately 8% of boys with hypospadias also have a UDT. The more severe the hypospadias, more are the chance of having associated UDT; studies show that about 5% of distal hypospadias may have UDT, while up to 32% of severe hypospadias are associated with UDT. **Fig. 1.4a, b** and **Fig. 1.5** show distal and midpenile hyposapdias. **Fig. 1.6** and **Fig. 1.7a, b** show severe hyposapdias with bilateral descended gonads. **Fig. 1.8** shows severe hyposapdias with unilateral nonpalpable gonad, to be investigated for DSD.

Prostatic Utricle

Prostatic utricle or vaginal pouch is a homolog of the vagina in males. Enlargement of the utricle has been noted in boys with hypospadias, and

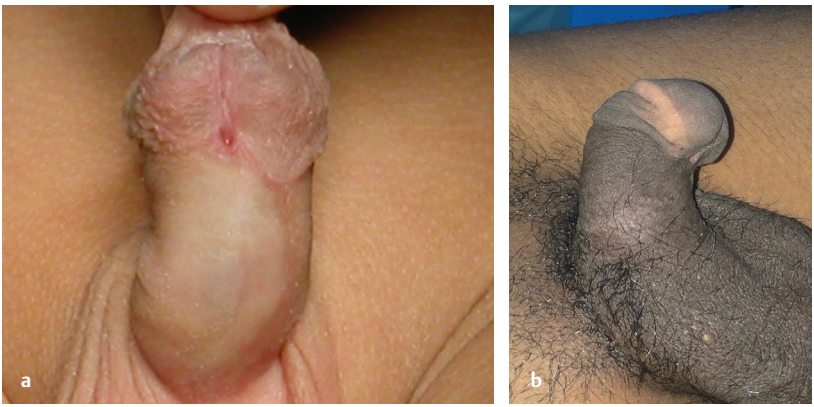

Fig. 1.4 (a) Distal hypospadias. Note the meatus at the corona, with well-developed ventral penile tissues. There is no significant chordee. **(b)** Distal hypospadias in 17-year-old adolescent boy. Note the significant ventral curvature.

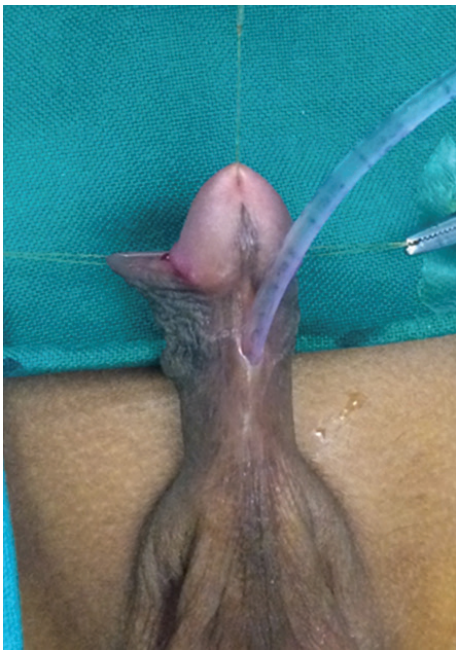

Fig. 1.5 Midpenile hypospadias. Note the poor urethral plate.

Fig. 1.6 Severe hypospadias. Note the scrotal opening, small phallus, severe chordee, and a generalized hypoplasia of ventral penile tissues.

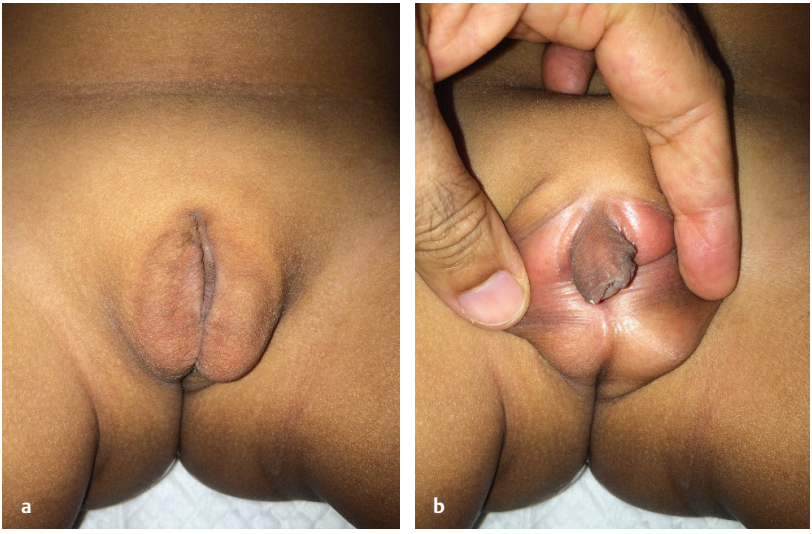

Fig. 1.7 (a) Severe hypospadias with severe penoscrotal transposition giving a female phenotype appearance. **(b)** Separating the labioscrotal folds reveals a small phallus, severe hypospadias, and bilateral gonads in labioscrotal folds.

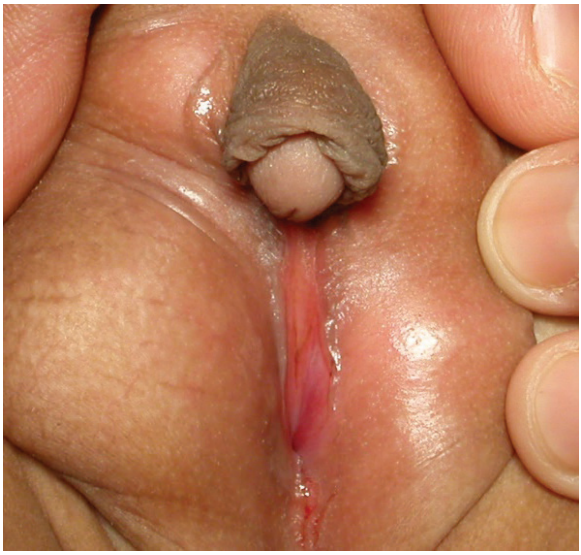

Fig. 1.8 Mixed gonadal dysgenesis presenting with severe hypospadias, right descended gonad, and nonpalpable left gonad. The karyotype was mosaic (46XY/45XO).

may be because of deficient action of mullerian inhibiting factor. Most of the enlarged prostatic utricles are found in proximal and severe hypospadias, occurring in about 11% of such severe cases. In the most severe cases, it may even open onto the surface on the perineum (**Fig. 1.1**). Enlarged utricles may result in urinary tract infection, and a large utricle may compress the urethra and result in difficulty in voiding or urinary retention. In addition, a common practical problem during operation for severe hypospadias is that an enlarged utricle may cause difficulty in passing the catheter into the bladder.

Disorders of Sex Development

Hypospadias and DSD may occur as a spectrum. In general, the chance of a child with hypospadias having a DSD increases with an increased severity of hypospadias especially with scrotal or perineal hypospadias.

Thus, in a child with hypospadias, the possibility of associated DSD should be considered in the following cases:

a. Severe hypospadias or hypospadias with small phallus (micropenis).
b. Hypospadias with associated UDT, especially if the UDT is nonpalpable, the risk of DSD may be as high as 50%. The most common diagnosis is mixed gonadal dysgenesis (MGD; **Fig. 1.8**), followed by ovotesticular DSD (which is much less common). The diagnosis of MGD is suspected clinically when there is severe hypospadias with unilateral nonpalpable UDT. Karyotype showing 46XY/45XO mosaic pattern confirms the diagnosis. The management depends on the age at diagnosis, if sex of rearing has already been established. It is recommended to remove the dysgenetic (streak) ovary present in the abdomen by laparoscopy. The need to remove mullerian remnants (usually seen as a hemiuterus-like structure) is not clear, although malignant transformation of retained mullerian structures has been reported in other conditions.

Any child with above features should be investigated for DSD, using a karyotype and other investigations.

Malformation Syndromes

Over 90% of cases of hypospadias occur as an isolated anomaly. However, a number of syndromes may be associated with hypospadias. Syndromic hypospadias is suspected with dysmorphic facies, developmental delay, microcephaly, and/or anorectal malformation. A few examples are given below:

Smith-Lemli-Opitz Syndrome

This results from an autosomal recessive mutation of the *DHCR7* gene on chromosome 11q13 coding for 7-dehydrocholesterol reductase; multiple congenital anomalies are attributed to this single metabolic defect. This autosomal recessive condition occurs in 1:20,000 births, ranking it third in prevalence among whites, behind cystic fibrosis and phenylketonuria. Affected individuals have impaired cholesterol synthesis because of

deficiency of 7-dehydrocholesterol reductase, resulting in mental retardation, facial deformities, microcephaly, syndactyly, and genital anomalies. The spectrum of external genital findings in males ranges from a female phenotype to hypospadias with cryptorchidism.

G Syndrome (Opitz G/BBB Syndrome)

This includes both X-linked and autosomal dominant forms: X-linked mutations in the midline-1 gene or autosomal dominant deletions in chromosome 22q11. The resultant phenotype includes hypertelorism, tracheoesophageal defects, cleft lip/palate, and mild mental retardation. Mild-to-moderate mental retardation and swallowing problems causing aspiration may also occur.

WAGR Syndrome

WAGR syndrome (Wilms' tumor, aniridia, genital anomalies, mental retardation) results from a deletion in chromosome 11p13.

13q Deletion Syndrome

It is characterized by mental retardation, facial dysmorphia, imperforate anus, penoscrotal transposition, and hypospadias (**Fig. 1.9a**, **b**).

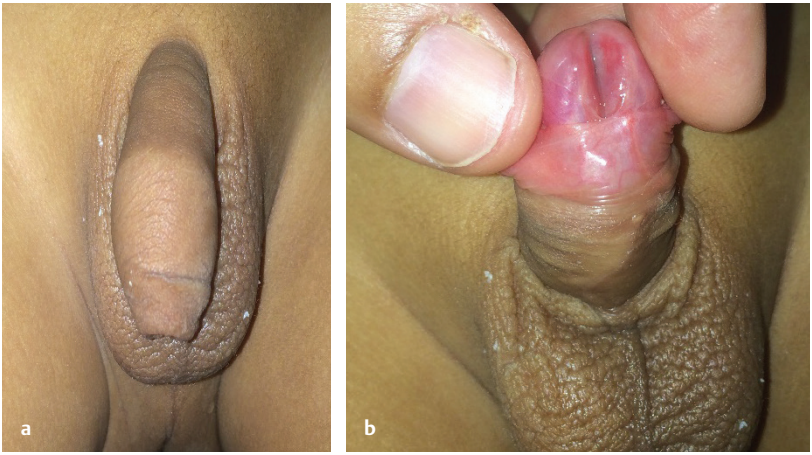

Fig. 1.9 Megameatus intact prepuce (MIP) variant of hypospadias. **(a)** The normal prepuce and **(b)** the coronal hypospadias are seen on preputial retraction.

Hand-Foot-Uterus Syndrome

This is an autosomal dominant condition due to mutations in the *HOXA13* gene on chromosome 7p14-15 resulting in bilateral thumb and great toe hypoplasia.

Wolf–Hirschhorn Syndrome (Pitt's Syndrome)

This is a microdeletion syndrome due to deletion on the short arm of chromosome 4. The characteristic features are craniofacial anomalies (microcephaly, micrognathia, hypertelorism, and periauricular tags), growth retardation, intellectual disability, hypotonia, seizures, congenital heart defects, hypospadias, and other anomalies. Antibody deficiencies are also common.

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