

Review Article

Hypospadias: a review

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ABSTRACT

Hypospadias is a congenital malformation of the male external genitalia, which includes: anomalous location proximal to the urethral meatus, in any portion of the glans penis and perineum, hooded dorsal foreskin, and inverted penile curvature on the dorsal side of the foreskin. The etiology has been considered multifactorial, secondary to the interaction of environmental factors with specific genetic background. It represents the second most frequent congenital defect in male newborns. It has increasing prevalence rates of 0.25 new cases per 10,000 newborns per year. Risk factors that have been identified include infants small for gestational age with weight below the 10th percentile, head length and/or circumference, intrauterine growth restriction, and placental insufficiency. Regarding environmental risk factors, maternal exposure to pesticides has been linked. Prenatal diagnosis has been described, however proximal hypospadias is usually detected, making it difficult to diagnose distal hypospadias using this method. So usually the diagnosis is made after birth during the physical examination. To date, more than 300 surgical techniques are known for the correction of hypospadias. The treatment of distal hypospadias is currently performed in one time; the management of proximal hypospadias is controversial; one group favors the one-stage procedure, while other groups choose to perform the two-stage procedure.

Keywords: External genital development, Pediatric surgery, Pediatric urology, Hypospadias, Hypospadias repair, Hypospadias complications

INTRODUCTION

The term hypospadias, coined by the physician and philosopher Galen in the 2nd century BC. It comes from the Greek Hypos-underneath and Spadon-crack or hole. It is a congenital malformation of the male external genitalia, characterized by a classic triad, which includes: anomalous proximal location of the urethral meatus, in any portion of the glans penis and perineum, hooded dorsal foreskin, and an inverted penile curvature on the dorsal side of the

foreskin. Secondary to inadequate growth of the urethral fold and ventral prepuce of the penis. The first description and its surgical correction were reported by the Roman surgeons Heliodorus and Antillus in the 2nd century AD.¹ The etiology of hypospadias has been considered multifactorial, secondary to the interaction of environmental factors with a specific genetic background.² Androgens and estrogens play a crucial role in genital development, in case of imbalance, congenital malformations of the penis can be observed.³ A recent

study showed that estrogen and androgen signaling are intrinsically necessary for normal closure of the urethra.⁴

Development of the external genitalia occurs through three main pathways: androgen independent, androgen dependent, and endocrine/environmental influence.⁵

The first phase occurs in the absence of hormonal stimulation, between the fifth and eighth week of pregnancy. During this phase, the cloacal folds are formed, formed by the mesodermal cells, oriented laterally to the cloacal membrane. These folds join anteriorly to create the genital tubercle (GT), composed of three cell layers: the lateral plate mesoderm, the superficial ectoderm, and the endodermal urethral epithelium. They then rupture posteriorly into the urogenital and anal folds that surround the urogenital sinus. In males, the second phase, dependent on hormones, begins with the development of the gonads. Two of the most significant actions of testicular testosterone are elongation of the TG and formation of the urethral depression. The urethral plate, the distal section of the urethral groove, is delineated laterally by the urethral folds and extends toward the glans penis. The urethra is generated when the urethral folds fuse and the penile sheath is created from the outer surface of ectodermal cells, which fuse with the ventral part of the phallus to form the median raphe. Various malformations, including hypospadias, abnormal curve of the penis, and inappropriate generation of the foreskin, may be caused by a genetic disruption or change in signaling pathways in the development of the male external genitalia and urethra, leading to abnormal closure, or incomplete urethral.³

The precise etiology of hypospadias is not yet known. However, there is increasing evidence that exposure to endocrine-disrupting chemicals (EDCs) such as pesticides, phthalates, bisphenol A, and pharmaceutical hormone compounds such as diethylstilbestrol; they influence the hormonal signaling pathways involved in fetal development, generating hypospadias. Factors such as diethylstilbestrol do not have the ability to affect DNA sequence (i.e., genetic mutations), but have been shown to promote epigenetic alterations.^{6,7}

Epidemiology and risk factors

Hypospadias is the most common penile malformation; It represents the second most frequent congenital defect in male newborns, its frequency has increased in recent decades by 11.5%.⁷ Increasing prevalence rates of 0.25 new cases per 10,000 newborns per year have been reported in the literature, secondary to a probable environmental association.⁸

The risk of it occurring in an infant if his father has hypospadias is 8% and 14% if a sibling has the condition; if two members of the same family have hypospadias, the risk is about 21%.⁹

Risk factors that have been identified include small-for-gestational-age newborns with weight below the 10th percentile, head length and/or circumference, intrauterine growth restriction, as well as placental insufficiency as with the use of reproductive technologies. assisted.¹⁰ Regarding environmental risk factors, maternal exposure to pesticides has been linked.¹¹ In a recent study, conducted by Das et al, 30.1% of all pregnancies had probable endocrine disrupting (ED) exposure. Maternal exposure to DE during the first trimester significantly increased the risk of having a child with hypospadias (OR=4.72 (95% CI: 2.10 to 10.60)). The most frequent occupations conferring possible exposure, were related to farm activities. Parental occupational exposure to pesticides was associated with at least a two-fold increased risk of hypospadias.¹²

Molecular bases and/or genetic analysis

To date, 26 genes associated with hypospadias have been reported (Table 1).¹³⁻²²

Genome-wide association studies (GWAS) suggested that less than 10% of patients with hypospadias had associated genetic mutations; however, more recent studies using next-generation sequencing have increased detection rates by up to 30% of cases.^{2,23}

CLASSIFICATION

The classification of hypospadias is divided into distal, medial, or proximal, with subdivisions based on the location of the urethral meatus (Figure 1). This classification was suggested by Duckett in 1989. 70% of hypospadias will correspond to glanular.⁹

Associated malformations

Among the most common associated anomalies in patients diagnosed with hypospadias are cryptorchidism, inguinal hernia, and hydrocele. Approximately 7% of patients with hypospadias have cryptorchidism; in posterior hypospadias, the incidence of cryptorchidism may increase to 32%. Inguinal hernia occurs in up to 17% posterior hypospadias, 8% medians and 7% anterior.³

Urinary tract malformations are associated infrequently because the external genitalia develop later in gestation than the upper urinary tract. Various series have reported an incidence of 1% to 3% of genitourinary anomalies in association with hypospadias; Among the most frequent are unilateral renal agenesis, ureteropelvic junction obstruction, and mild vesicoureteral reflux. When other systems are involved, the incidence increases to 7%. Up to 14% of hypospadias and up to half of perineal hypospadias have a Müllerian remnant, which causes difficulties in catheterization, urinary obstruction, or urinary tract infections (UTI) after repair; most of them can be identified by ultrasound.²⁴

DIAGNOSIS

Prenatal diagnosis is not common, due to the subtle findings of mild and moderate types that can be easily missed. It generally depends on indirect ultrasonographic signs that are a consequence of the distal urethral defect. Ultrasound findings are blunt penile tip, two longitudinal echogenic lines on the lateral sides of the penile tip that correspond to the dorsal hood, ventral shortening, curved penile shaft located between the two scrotal folds, tulip sign, and abnormal urinary flow managed.²⁵ Due to what has been mentioned regarding prenatal diagnosis, in most cases the diagnosis is made after birth during the physical examination, where a deficiency of the ventral skin can be observed with a dorsal hood of the prepuce and an abnormally located meatus with varying degrees of ventral curvature of the penis.²⁶

Initial evaluation should include serum electrolytes, 17-hydroxyprogesterone (17-OHP), karyotype, abdominal ultrasound, urinary system, and internal genitalia to assess Müllerian structures and associated malformations. It is important to carry out this diagnostic approach, since in cases of proximal hypospadias associated with unilateral or bilateral non-palpable cryptorchidism, disorders of sexual differentiation are observed in 17-29% of patients, which will set the standard for treatment, requiring multidisciplinary management.^{3,27}

TREATMENT

To date, more than 300 surgical techniques have been described for the correction of hypospadias. All of them, having the same objective: that the meatus be located at the tip, achieve a straight penis, uninterrupted urinary flow, and that the child recovers his self-confidence, achieving adequate aesthetics. In case the surgery is performed in adulthood, correct reproductive problems due to difficulty with sperm deposition; curvature correction that causes difficulties during sexual intercourse and decreased pleasure with genital appearance.²⁸ The use of magnification, the atraumatic manipulation of the tissue, the use of delicate surgical material, the types of suture and adequate hemostasis are fundamental requirements, which influence the surgical result.³ The treatment of distal hypospadias, is currently performed in a time, some of the most used techniques are the transverse incised plate (PIT), the Mathieu island flap and Onlay. The management of proximal hypospadias is controversial; one group favors the one-stage procedure, while other groups choose to perform the two-stage procedure. Some of the factors that could affect the outcome of the repairs are the site of the meatus, the severity of the cord, the adequacy of the foreskin skin, and the existence of penoscrotal transposition.²⁹ The Glans-Urethral Meatus-Shaft Score (GMS) is a concise and reproducible way to describe the severity of hypospadias before surgery, to predict the outcome of surgery. Integrates the results of the physical examination in the operating room, evaluating the quality of the glans and urethral plate, the position of the urethral

opening, and the degree of penile curvature.³⁰ Shoukry et al carried out a study where they observed that patients with a high GMS score (greater than 6) have a higher risk of complications and patients with a glans penis of 14 mm or more and a penoscrotal length of 5 cm or more are associated with a lower risk of complications.³¹

Role of preoperative hormone therapy

In 1970, the use of preoperative hormone therapy in hypospadias surgery to improve surgical results was first proposed.³² Currently, although there are no defined guidelines for its use, preoperative androgen stimulation in the form of systemic testosterone, topical testosterone, and derivatives (human chorionic gonadotropin, dihydrotestosterone) have been used to stimulate glans size prior to surgery, which allows a better tubularization of the urethral plate and decreases the incidence of glans dehiscence. Therapy should be stopped 1-2 months before surgery to avoid adverse effects during or after surgery.²⁶

When to perform the surgery?

The American Academy of Pediatrics recommends performing surgical repair from 6 to 18 months of age. However, some studies show a minimal complication of the repair in patients 4 to 6 months of age.³³ Prior to surgery, it is important to perform a detailed physical examination, focused on the findings that will guide the surgeon in order to carry out an adequate surgical plan (Table 2).²⁶ Aesthetic risks, age-dependent tissue diameters, and the emotional repercussions of genital surgery are all factors that have an impact.³⁴

Surgical principles of hypospadias

As previously mentioned, the surgical correction of hypospadias can be in one or two times, this will depend on the type and the decision of the surgical team. However, the following steps must be followed, regardless of whether the surgery is performed in one or two stages Table 3.²⁶

Orthoplasty or corporoplasty

Penile curvature is clinically addressed with the degree of severity, cause, and management is subsequently defined. It is estimated that approximately 7% of hypospadias do not have curvature.³⁵ It has been defined as the curvature of clinical significance, a curvature greater than 30°. Springer et al conducted a study in 2011, where they applied anonymous questionnaires to pediatric urologists, pediatric surgeons, urologists, and plastic surgeons from around the world. Finding that the consensus of clinical significance regarding penile curvature is respected worldwide. In curvatures of 10° and 20° in 68.9% and 64.2% respectively, they did not perform correction. In contrast, in curvatures greater than or equal to 30°, various correction techniques were performed as they were considered clinically significant.³⁶ The causes of penile

curvature are: scant ventral skin, presence or absence of cordee, short urethral plate, and disproportion of the corpora cavernosa. The evaluation of the degree of penile curvature represents a challenge, since imprecision and variability between observers are obstacles, which affect the proper use of surgical management algorithms.³⁵ Degloving of the penis is an essential first step of orthoplasty. Other orthoplasty maneuvers, such as proximal ventral dissection (PVD) down to the bulbar urethra and release of the lateral fibrous junctions, may be added, depending on the severity of the ventral curvature. PVD has been used as an additional step to degloving to achieve further straightening of the penis before attempting more radical maneuvers such as urethral plate lift, transection, and corpora cavernosa grafting.³⁷

Urethroplasty

The second step consists of urethroplasty, which will also require clinical evaluation. A measurement of the urethral plate will be made from the hypospadiac meatus to where the neomeatus will be, as well as a measurement of the width of the glans penis and the width of the urethral plate, since these are predictive factors for complications, mainly dehiscence and urethrocutaneous fistulas. Evaluation of the urethral plaque cleft is important; urethral plates that have pronounced indentations have better results than those that are completely flat.³⁸ There is a wide diversity of surgical techniques to perform urethroplasty, which will depend on the location of the hypospadias and individualized clinical evaluation (Table 4).³⁹⁻⁴⁵

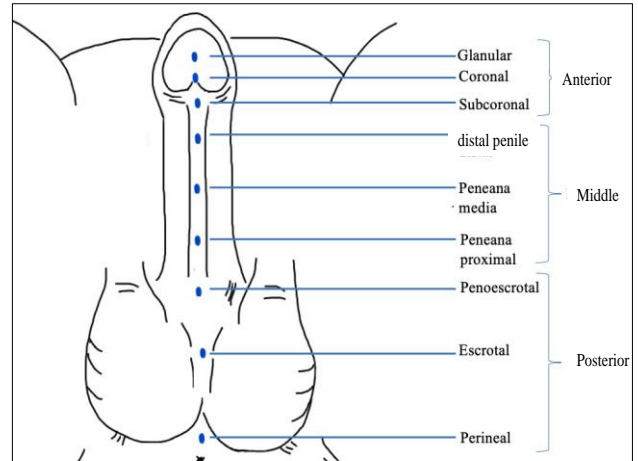


Figure 1: Classification of hypospadias.

Skin plasty

The skin of the penis is a flexible and androgen-dependent tissue, characteristics that are favorable for covering. The choice of surgical technique will depend on the patient's skin, there are options such as the Bayer flap, z-plasty and the inverted Omega incision, among others.⁴⁶ To assess cosmetic results after the surgical procedure, there are currently several validated scores, such as the pediatric penile perception score (PPPS), the hypospadias objective score (HOSE) assessment, and the hypospadias penile objective assessment (HOPE).³¹

Table 1: Hypospadias and genetics.

Study	Associated gene
Zhou et al	Variations in the TGFB1 gene and its receptors increase the risk of hypospadias
Wang et al	Increased expression of the HOXA13 gene in the foreskin and urethra in patients with hypospadias
Samtani et al, Wang et al	Mutations in SRD5A2, a gene involved in the conversion of testosterone to dihydrotestosterone, have been linked to an increased risk of hypospadias
Beleza-Meireles et al	Genetic variants of ATF 3 in patients with hypospadias
Kalfa et al	ATF3 overexpression in the urethral plaque in hypospadias
Beleza-Meireles et al	Estrogen receptor 2 (ERβ) gene
Beleza-Meireles et al	FGF8 and FGFR2 mutations in patients with hypospadias
Liu et al	Activating transcription factor 3 (ATF 3) is upregulated in hypospadias tissue
Petiot et al	The FGF receptor 2 (FGFR2) gene contributes to the closure of the urethra through interaction between the epithelium and the mesenchyme. Abnormalities in the expression of FGFR2 result in hypospadias

Table 2: Anatomical presurgical considerations for hypospadias.

S. no.	Pre-surgical considerations for hypospadias
1	Location of the meatus
2	Presence and degree of ventral curvature
	Mild <30°
	Moderate 30-60°
3	Severe >60°
	Penile rotation
	Mild < 30°

Continued.

S. no.	Pre-surgical considerations for hypospadias
	Moderate 30-60°
	Severe > 60°
4	Quality (width and depth) of the urethral plate
5	Size of the glans penis and depth of the navicular fossa
6	Degree of deficiency of ventral skin
7	Scrotal abnormalities such as penoscrotal transposition and bifid scrotum
8	Availability of the foreskin
9	Penile length

Table 3: Surgical principles for hypospadias.

Surgical principle	Characteristics
Orthoplasty or corporoplasty	Rectification is performed and the shaft of the penis is brought to an acceptable angulation value or 0°
Ureteroplasty Spongioplasty Glanduloplasty	Locate meatus in functional, anatomical and aesthetic position using different techniques
Skin plasty	Coverage of the shaft of the penis after correction of curvature and localization of the meatus hyospa

Table 4: Techniques described for urethroplasty in hypospadias.

Techniques for subcoronal distal hypospadias	Type of hypospadias in which it is used
Meatal advancement and glanduloplasty (MAGPI)	Mathieu (can be used up to distal third hypospadias)
One time techniques	
Tubular incised plate (TIP)	Distal, middle, proximal, penoscrotal, and scrotal* hypospadias, second stage
Koyanagi	Distal, middle third and proximal hypospadias
Island foreskin flap	Distal, middle third, proximal, penoscrotal, scrotal hypospadias
3 in 1 (Two flaps plus a graft)	Median, proximal, penoscrotal, and scrotal hypospadias
Asopa-Duckett	Proximal, penoscrotal, scrotal, and perineal hypospadias
CPI onlay-inlay/onlay-tube-onlay	Proximal, penoscrotal, and scrotal hypospadias, operation on stenosis
Two-stroke techniques	
2 times with Belt flap	Proximal, penoscrotal, scrotal, and perineal hypospadias
Cloutier o Turner-Warwick	Proximal hypospadias, penoscrotal scrotal and perineal
2 times with graft	Proximal, penoscrotal, scrotal, and perineal hypospadias

Table 5: Main post-surgical complications.

S. no.	Main post-surgical complications
1	Urethrocutaneous fistula
2	Urethral stricture
3	Balanitis xerotica obliterans of the urethra leading to stricture
4	Meatal stenosis
5	Aesthetic problems
6	Glans dehiscence
7	Urethrocele
8	Aesthetic problems
9	Recurrent or persistent penile curvature
10	Misdirected urinary stream
11	Erectile dysfunction

Complications

Complications can occur in 5-10% of patients with distal variants and 15-56% of patients with proximal forms, according to most short-term estimates (Table 5).²⁶ Acute complications occur 7-10 days after the surgical procedure, some of them are hemorrhage, hematoma, edema, wound infection, wound dehiscence, skin necrosis, flap necrosis, fistula, torsion of the penis, penile erections, involuntary withdrawal of the urethral catheter, bladder spasms. Fistula being the most frequent complication.²⁸ Postoperative complications can usually occur in the first few months after surgery. However, long-term follow-up is mandatory, since late presentations with a urethral fistula and recurrent curvature of the penis after puberty have been documented.³⁴

DISCUSSION

A meticulous pre-surgical approach in hypospadias is highly relevant, since it will have an impact on the decision of the most appropriate surgical technique, as well as on the aesthetic and functional results for the patient. Currently, predictive associations that could affect decision making are still being investigated. New technologies using artificial intelligence have shown promising results, providing an objective assessment and acting as an expert assessor of phenotypes. Fernandez carried out a study where they used pixel analysis, concluding that the current phenotyping of hypospadias using only anthropometric variables, can be expanded to include histological correlation and pixel analysis. Noting that pixel clustering has potential for a priori prediction of urethral plaque quality, beyond current subjective assessment.⁴⁷ Described in most reviews on hypospadias, is pre-surgical hormonal therapy, which was implemented since the 70's and is used to date due to its favorable results. However, there are no standardized guidelines for its precise indication, dosage, and duration of treatment. Di et al, carried out a systematic review of 25 studies with 4094 patients. Surgeons' criteria for using preoperative androgen stimulation varied, the most important being short penile length. The most frequently reported regimens for intramuscular (IM) testosterone were empiric monthly 2 mg/kg or 25 mg, and the duration was 2 to 3 months before surgery. Androgens were significantly effective in enhancing penile development, with changes commonly peaking at 2-3 months. The effects of preoperative hormone therapy on complications are controversial, and possible causes include hormone sensitivity, degree of hypospadias, surgical techniques, and dosing regimens.⁴⁸ Assessment of penile curvature is a key component of hypospadias surgery. However, it represents a challenge due to the variability between observers of the methods used to measure it. Currently, applications have been developed to assess it. Cooper et al, conducted a study where calculating the radians of the hypospadias curvature by measuring the length and width of the arch did not improve interrater reliability. Demonstrating that the goniometer has the highest reliability in categorizing those with minimal (i.e., 15°) and more severe (i.e., >30°) curvature, but had poor interrater reliability (0.34-0.57) for those with moderate degrees of curvature. (16-30°).⁴⁹ Villanueva conducted a pilot study, where medical professionals (not urologists) were recruited to estimate curvature with an app-based method consisting of the Photoblend Pro app. Demonstrating better estimates of penile curvature using the app compared to the two most common methods currently used by pediatric urologists.⁵⁰ Weber et al retrospectively reviewed the records of 137 patients who underwent proximal hypospadias repair. Ventral curvature (CV), defined as mild (<30%), moderate (30%–45%), and severe (>45%), was recorded. before degloving, and after erection test. The percentage improvement in QoL and the need for further treatment (beyond degloving and proximal dissection) were assessed based on the preoperative degree of curvature. Degloving

associated with dissection of the proximal urethra was responsible for the improvement in the degree of curvature in 7 of 9 (77%) patients with mild CV, 23 of 44 (52%) with moderate, and 35 of 84 (40%) with serious CV. In addition, degloving was sufficient for VC correction in 7 of 9 (77%) mild cases, 14 of 44 (30%) moderate cases, and only 2 of 84 (2%) severe cases.³⁷ Regarding the surgical technique, there is controversy in the treatment using one or two times. Badawy et al carried out a study where they reported that patients operated on with the single-time technique had a success rate of 55% with a complication rate of 45%, being infection in (2.5%), partial dehiscence in (10%), urethrocutaneous fistula in (15%), meatal stenosis in (12.5%), urethral diverticulum in (5%). Patients operated by staged repair had a success rate after the second stage of 80%, complications were in the form of 4 fistulas (16%), hematoma and complete rupture in one case of reoperation (4%). Presenting a statistically significant difference in the incidence of complications between both groups in favor of a lower rate of complications (20%) in the group by stages versus the group by stages (45%) with $p=0.0419$.⁴²

As hypospadias surgery has evolved, different and sometimes complex post-surgical bandaging methods have been used. However, there is no strong evidence to support the superiority of one type of dressing over another or whether postoperative dressing offers any advantage over no dressing. Aldabek et al conducted a study retrospectively reviewing a database for patients who underwent hypospadias repair between 2013 and 2021. Patients in the one-diaper technique received the same type of dressing and discharge instructions as those in the double diaper group, except for leaving the catheter draining freely in a single diaper. Where they observed that there were no statistically significant differences in surgical site infection, urinary infection or wound dehiscence between the two groups. The incidence of meatal stenosis (8.3 versus 1.4%, pZ 0.044) and fistula formation (15.3% versus 5.4%, pZ 0.037) was significantly higher in the double diaper group than in the single diaper. respectively. Concluding that the single diaper technique, after hypospadias repair, is not associated with a higher risk of complications compared to the double diaper technique.⁵¹

CONCLUSION

Hypospadias is a frequent malformation, which may or may not be related to other genital and urinary malformations, and even to disorders of sexual differentiation. That is why an adequate clinical history should be taken, investigating associated risk factors. It is important to carry out a thorough physical examination, making an intentional search for associated malformations, such as inguinal hernia, hydrocele, and cryptorchidism, which in case of being bilateral, we must suspect alteration in sexual differentiation. With the development of new technologies, predictive associations have been investigated that could help decision-making for

the choice of the most appropriate surgical technique for each case.

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