International Surgery Journal
Rodríguez Martínez ADC et al. Int Surg J. 2024 Aug;11(8):1439-1443
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

Review Article

DOI: https://dx.doi.org/10.18203/2349-2902.isj20242149

Hypospadias: a review

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Received: 10 July 2024
Accepted: 25 July 2024

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ABSTRACT

Hypospadias is a common congenital anomaly, characterized by an alteration in the fusion of the ureteral meatus on the ventral aspect of the penis during embryogenesis. It presents with a classic triad of abnormal foreskin, penile curvature, and ureteral meatus in an ectopic position. Different types of hypospadias have been recorded, which will vary according to their severity and anatomical characteristics. Although its etiology has not been completely determined, it is known that it has a multifactorial origin, among which is genetic predisposition and has been associated with alterations in hormonal influence during pregnancy. An incidence of 1 in 200-300 male newborns has been reported. It has been associated with risk factors such as prenatal exposure to estrogens. It has been described concomitantly with other congenital anomalies such as Wilms tumor or aniridia. The initial management is surgical, which seeks penile anatomical correction and obtaining functional and aesthetic results. Currently, the surgical technique is recommended in a single surgical moment, which favors lower risks of complications. Prenatal diagnosis is of great importance with a post-birth evaluation to determine the type of hypospadias presenting and evaluate the most appropriate surgical approach. Surgical management must be accompanied by multidisciplinary management along with pediatrics and psychology, which resulted in a better physical and psychological outcome for the patient.

Keywords: Hypospadia, Ureteral meatus, Ectopic position, Utheroplasty, Hormonal influence

INTRODUCTION

Hypospadias is the most prevalent genitourinary congential alteration in male fetuses after undescended testicle, resulting from a poor fusion of the urinary meatus in its midline on the ventral aspect of the penis during embryogenesis. Which is classically described by the triad of anomaly of the foreskin, penile curvature and blunt tip of penis.[1] Abnormal opening of ureteral meatus can be seen along the penis or even the perineum; greater penile curvature has been associated with patients with a more proximal opening. Historically, a higher rate of cases of hypospadias has been associated with premature patients, products of monochorionic twin pregnancies, children of mothers over 35 years of age or with low weight for gestational age.[2] Different classifications have been described based on the anatomical description, among which glandular hypospadias, hypospadias with distal division of corpus spongiosum, hypospadias with proximal division of the corpus spongiosum, and multi-operator hypospadias stand out (Table 1). Anatomically, these patients will present malformations along penis generally regardless of the type of hypospadias, among which is opening of the glans on its ventral side, opening

of the meatus on its ventral side, hypoplasia at the of the urethra, cutaneous urethral groove in its distal part and finally division of the corpus spongiosum behind ectopic meatus, frequently demarcated on skin of ventral aspect by a cutaneous relief, thus marking proximal beginning of malformation. Finally, because of previously described alterations, penile curvature is observed, which in most cases is attributed to an adhesion of the ventral skin to underlying structures. Additionally, an absence of frenulum artery is found.[3] Incidence of this congenital malformation if only male newborns are considered is between 1 every 200-300, for the most part, 70% represent mild to moderate cases, and only 30% of patients represent cases. more severe and more complex. Although exact etiology of this pathology is unknown, it is known that it is of multifactorial origin and there are different hypotheses that support its appearance, among which genetic predisposition and low influence on hormonal influence during embryogenesis stand out, which have been seen more related to anterior and medial hypospadias presentations. Transmission has been seen through both maternal and paternal inheritance with a heritability percent of 57-77%; However, causal genetic component has been demonstrated in only 30% of patients with malformation. Associated with hypospadias, a relationship has been found with appearance of other pathologies concomitantly which could be related to some genetic mutations, among those, the most related are Wilms tumor, aniridia, genitourinary malformations and mental retardation.[4] Some risk factors for presentation of hypospadias have been described, such as exposure during pregnancy to estrogens and anti-androgenic endocrine disruptions, in addition to being associated with shorter anogenital distance, which was also shown to be associated with exposure of mechanisms of action. androgenic, which associated with decreased fertility.

Table 1: Types of hypospadias according to their anatomical description.

Type of hypospadias	Characteristic
Glandular	Position of the ectopic meatus on the glans. Associated with severe meatal hypoplasia and significant penile curvature.
With distal division of corpus spongiosum	Related to greater adhesion to skin tissues of adjacent structures. It is associated with a slightly marked curvature of the penis.
With proximal division of corpus spongiosum	Related to greater adhesion to skin tissues of adjacent structures. It is associated with a very marked and severe curvature of the penis
Multi-operator	Multiple scar tissues, dehiscences, and reconstructed urethra are observed. Possible appearance of fistulas, meatal stenosis and unsatisfactory aesthetic results.

The management of hypospadias is surgical in nature which seeks adequate functionality of the penis as well as aesthetically successful results. Only at the end of the 20th century was it possible to understand the anatomy of the penis in patients with hypospadias. Beck and Thiersch in Germany, Mettauer in the United States, and Duplay in France were the first to describe the surgical principles in hypospadias correction surgery. It was not until 1970 that Leveuf-Petit-Cendron described the use of the multi-step surgical technique, however today the single-stage surgical technique is more frequently used.[3]

EMBRYOLOGY AND GENETIC ASPECTS OF THE PENIS

Penile embryological formation and development are mainly comprised of two steps which are accompanied by mechanisms regulated by different hormone-dependent or non-hormone-dependent molecules and by endocrinological processes involved in cell activation, differentiation and migration. Initially, for the formation of the primitive gonads, the migration of germ cells from the posterior surface of the yolk sac is generated and finally an invasion is created by the Wolffian mesenteric vessels, creating the signal for differentiation to the testicle. In addition, with the help of Leydig cells, the stimulation for the production and release of fetal testosterone will begin. If there is an error in these mechanisms, alterations in the genitals such as hypospadias or feminization of male genitalia are reported.[5]

For the formation of the external genitalia, a differentiation will be made depending on the genetic cascade that is activated or inactivated, accompanied by the induced hormonal influence. In the case of male patients, with the help of the Leydig cells responsible for the secretion of dihydrotestosterone, genital differentiation will be carried out with a growth of the genital tubercle, along with its elongation, while this elongation process is carried out secondarily. A space is created which will become the urethral groove which between weeks 9 and 12 will form the closure of the grooves that formed around the urethral groove and as a result the creation of the urethral canal. However, it is not until weeks 12 and 16 that this duct will become completely permeable to the penile tip through the invasion of ectodermal cells from this region (Figure 1). Miyagawa et al managed to define some genes involved in the differentiation and development of the external genitalia, among which is the sonic hedgehog (SHH) gene, which was found in the epithelium of the urethral tubercle in mice and its involvement was demonstrated in initial penile differentiation and cases of ambisexuality. Furthermore, its expression in the human fetal penis in the process of tubulization at week 14 of gestation was demonstrated through immunohistochemical studies. Haraguchi et al demonstrated that the absence of the SHH gene in mice resulted in a disruption in the development of the genital tubercle. In addition, a decrease in the

genes: WNT5A, Fibroblast growth factor 8 and 10, and BMP-2 and 4 was demonstrated when the SHH gene was absent. All these genes were shown to have implications in the differentiation, development and formation of external genitalia in mice. Finally, other mechanisms have been demonstrated by which they have been associated in a lower etiological percentage with hypospadias, among which genetic mutations and different receptors associated with the activation of the different signaling pathways stand out (Table 2).[1,6,7]

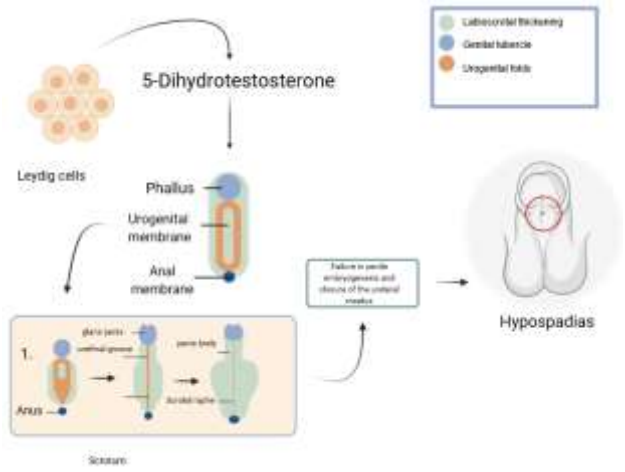

Figure 1: Embryogenesis of the penis.

Table 2: Genes associated with the etiology of hypospadias and its characteristics.

Gene	Characteristics
Estrogen receptor 2 (ERβ) gene	Genetic defects in this gene have been associated with cases of hypospadias
Activating transcription factor 3 (ATF3)	Dependent on estrogen response. It is increased and overexpressed in urethral plate in patients with hypospadias
SRD5A2	Responsible for the conversion of testosterone to dihydrotestosterone was associated with an increased risk of hypospadias
FGF8, FGFR2	Found in patients with hypospadias

EPIDEMIOLOGY

A prevalence of hypospadias has been reported in 1/200-300 live male newborns, among whom twin pregnancies represent an 8 times greater risk compared to non-multiple congestations.[1]

Yu et al they carried out a study in which they studied the prevalence and international trend of patients with hypospadias between the period 1980 and 2010 in more than 27 countries, where a prevalence of 20.9% per 10,000 births was found in the 27 countries during the period of set time. Furthermore, it was found that Latin American countries such as Argentina, Chile, Mexico, Colombia and Costa Rica, presented a lower total prevalence than countries in other regions, such as Italy, which presented a prevalence of 37.4% per 10,000 births. Finally, they concluded that during the period studied, an increase in the prevalence of hypospadias was observed and that possibly some factors related to the way in which previous cases of hypospadias and their follow-up were reported over time could have underestimated the prevalence of this pathology.[8]

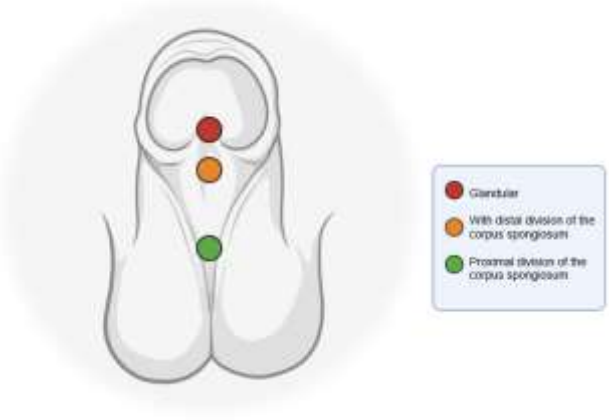

Figure 2: Types of hipospadias.

Table 3: GMS scale for evaluating the risk of suffering post-surgical complications.

Scale	Variables
G: Gland	Good size, healthy urethral plate, slight stretch marks.
	Suitable size, suitable urethral plate, with grooves.
	Small size, narrow urethral plate, some fibrosis.
	Very small size, no difference in urethral plate, very narrow.
M: Ureteral meatus	Glandular
	Coronal groove
	Mild or distal axis
	Proximal axis
S: Shaft	Uncorded
	Slightly corded (<30 degrees)
	Moderately corded (30-50 degrees)
	Severely chordate (>60 degrees)

CLINICAL MANIFESTATIONS

Commonly, upon clinical evaluation, hypospadias is defined as the combination of 3 anatomical findings which are the abnormal urethral opening of the penis on its ventral side, abnormal distribution of folds, and abnormal ventral curvature.[4] It is of great importance to determine the phenotype and classification. of hypospadias to carry out the most appropriate

management. I must emphasize mainly the location of the meatus, degree of penile curvature and visualization of tissue underlying the penis such as scrotum. Depending on the characteristics of each item, its risk of post-surgical complication can be determined with the help of the GMS scale (Table 3). Which associated between a higher score represents a greater risk of complications (Figure 2).

DIAGNOSIS

During pregnancy, the external genitalia will vary depending on the week of gestation. Using ultrasound, some parameters can be observed that could indicate a penile abnormality. It is known that at week 20-22 the distinction of the fetal scrotum and some penile structures is already achieved, among which the corpora cavernosa is observed, whose edges can be delimited by ultrasound using an echogenic interface. Because the urethra contains urine, the anechoic duct can be observed. As the weeks of gestation pass, a three-dimensional or two-dimensional ultrasound could be used to observe the meatus more specifically. Scrotal descent will only occur until week 25-27, which can be observed as echogenic oval structures in the scrotal sac.[9] Finally, the diagnosis is more frequent in the third trimester of pregnancy; However, during previous ultrasounds some findings or anomalies could raise suspicion about the possible diagnosis, in those cases where the ultrasound from 28 weeks of gestation shows a penile anatomy with characteristics of a curved penis, with a blunt tip and Abnormal foreskin should raise suspicion of a possible diagnosis of hypospadias. Additionally, the diagnosis has been supported along with the ultrasound characteristics already mentioned, the appreciation of fetal urination, which is very useful to confirm the suspicion of hypospadias when observing an abnormal urinary stream. The usefulness of magnetic resonance imaging in the diagnosis of hypospadias has also been discussed. However, little cost-effective utility has been shown due to the impossibility of evaluating the voiding stream in vivo, higher costs, and the low availability of images.[1]

Some complementary laboratory tests have been described that could help with the diagnosis of hypospadias, among which is the quantification of testosterone, FSH/LH and anti-Müllerian hormone (AMH). In addition, other cytogenetic studies of karyotype, in situ hybridization, among others, could guide a little more about the possible origin of this pathology in the patient.[3]

TREATMENT

The management of choice for hypospadias is surgical, which seeks as its goals to obtain a sexual organ that is functional, without curvature and with a ureteral meatus with laminar flow and aesthetic appearance. It is recommended to perform the surgical intervention between 6-12 months of age. A preoperative evaluation must be carried out exhaustively to understand the anatomy and type of hypospadias in the patient to achieve the best result by selecting the most appropriate surgical approach, since all hypospadias repairs are unique and adaptable. to your needs. This surgical procedure must be performed in 3 moments, which will begin with the undressing of the penis and exposure of the corpus spongiosum, to continue with the reconstruction of the flat ventral aspect with the possibility of performing mammoplasties, plastic glands, among others. and finally, a plasty of the cavernous bodies is performed to correct the ventral curvature of the penis.[3]

Most patients undergoing penile reconstruction with hypospadias will require extra skin grafts to restore the remaining urethra. The use of autografts from skin around the genital area has been considered; However, they have not been very successful, which led to the search for new options such as the use of tissue engineering with the production of tubular tissue with the ability to generate angiogenesis at the ureteral level.[10] In recent years, this science has attracted attention, which seeks the production and subsequent replacement of tubular organs in those patients with dysfunction or absence of some organ or tissues. Using stem cell cultures to produce organs, beneficial results and positive evolution of patients who have benefited from this technology have been successfully described. However, it is an area that is still developing and needs new studies to verify its long-term effects. Fortunately, for patients with hypospadias, in this process of developing new fabrics, significant advances have been generated in recent years, generating a focus mainly on the development of urethral mucosa taking into account characteristics in which these tissues can be vascularized, biodegradable and biocompatible.[11,12] Although it is unknown what is the ideal combination of materials for the reproduction of these tissues in the repair of hypospadias, it seems that the most optimal are through the seeding of different cell types, which include stromal cells and epithelial cells.[13] Cao et al performed ureteral reconstruction in 30 rabbits using a scaffold composed of silk fibroin called BAM hydrogel, which was previously revascularized. They finally determined that epithelial regeneration of the urethra and smooth muscle was obtained. In conclusion, it was determined that those patients with larger defects benefit from pre-seeded scaffolds, unlike those with smaller defects who do not need these techniques.[10] It is known that in the case of patients with hypospadias, the production of a completely impermeable scaffold is sought, among other characteristics. To date, the ideal material for these patients has not been reported, even so there are materials with promising results in terms of functionality and usefulness in reconstruction, such as the use of the submucosa of the small intestine of pigs in the application of engineering. tissues for ureteral reconstruction, promising material, but still with the need to carry out new studies.[14]

Among the possible post-surgical complications are early bleeding and hematoma, and meatal stenosis, the formation of enterocutaneous fistulas, the formation of urethral diverticula, poor healing and failure in reconstruction have been described late. functional. The formation of enterocutaneous fistulas was reported among the complications with the highest prevalence of 21%, which occurred more frequently during the first 4 weeks after surgery.[2]

CONCLUSION

The management of hypospadias involves a multidisciplinary approach ranging from prenatal evaluation to specialized surgical intervention. Reconstructive surgery, ideally performed between 6 and 12 months of age, seeks not only to correct structural anomalies, such as malformation of the urethral meatus and penile curvature, but also to ensure an optimal functional and aesthetic result. Early identification and proper management of this congenital condition are crucial to minimize complications and improve the quality of life of patients suffering from this malformation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Rodríguez Martínez ADC, Barrientos-Villegas S, Mondragón CFM, Hernández EF, Martínez-Sosa IP, Mera BB, et al. Hypospadias: a review. Int Surg J 2024;11:1439-43.