

HYPOSPADIAS. ANATOMY, EMBRYOLOGY, AND RECONSTRUCTIVE TECHNIQUES

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ABSTRACT

Hypospadias is one of the most common congenital anomalies that can be treated with surgical reconstruction. The etiology in the majority of cases of hypospadias remains elusive. Androgens are clearly critical for penile development; however, defects in androgen metabolism and/or the androgen receptor explain only a small subset of patients with hypospadias. This paper reviews the present strategies to understanding the etiology of hypospadias. This is followed by a review of the anatomy of the male and female genitalia with an emphasis on reconstructive implications. Finally, current techniques for hypospadias repair are reviewed.

Key words: hypospadias; anatomy; embryology; surgical technique; congenital anomalies
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INTRODUCTION

Hypospadias is one of the most common congenital anomalies occurring in approximately 1:250 to 1:300 live births. In patients with severe hypospadias the genitalia may look ambiguous at birth resulting in emotional and psychological stress for parents in that the gender assignment of their baby immediately comes into question. Left-uncorrected patients with hypospadias may need to sit down to void and tend to shun intimate relationships because of the fears related to normal sexuality.

INCIDENCE

In Europe the prevalence of hypospadias in the 1970's and 1980's has been increasing with no obvious explanation. In the United States data from two birth defects surveillance systems has also shown an unexplained doubling in the incidence of hypospadias (1). The U.S. study from the Center of Disease Control is particularly intriguing in that the incidence of severe hypospadias, not just mild forms, is increasing implying that the increase in hypospadias is not secondary to an increase in surveillance or reporting.

ETIOLOGY

Androgen Metabolism

Normal sexual differentiation is dependent on testosterone and its metabolites along with the presence of a functional androgen receptor. Genetic defects in the androgen metabolism pathway (i.e. 5- α -II reductase defects or androgen receptor defects) are known to result in hypospadias. Although abnormalities in androgen metabolism can result in severe hypospadias this does not explain the etiology of moderate and mild forms of hypospadias (2-5).

Abnormal Cellular Signaling

We propose an alternative hypothesis whereby hypospadias occurs by abnormal cellular signaling between tissues of the phallus during development. This hypothesis has been pursued by first defining the ontogeny of epithelial and smooth muscle differentiation markers in the developing male and female genitalia (6). The original work has been extended to anatomical studies of hypospadias and the anatomy of the clitoris (see below). Specifically, emphasis has been given to reconstructive strategies

for penile curvature and feminizing genitoplasty surgery based on the anatomical studies (7,8).

We have also focused on penile growth and differentiation. A number of important questions concerning penile growth remain unanswered. For example, the testosterone pathway and specifically DHT are critical for penile growth and differentiation. However, what about other non-androgen independent growth factors such as the insulin growth factor family. A model to study human penile growth has been designed to begin to answer some of these questions (9).

of male urethral development proposes that the urethral plate is elevated by urethral folds, which fuse ventrally in a proximal to distal sequence. Unlike its proximal counterpart, the urethra, which forms within the glans, is lined by a stratified squamous epithelium and has a more controversial development. One theory supports the idea that fusion of the urethral folds extends all the way to the tip of the glans. Another theory suggests that a solid ectodermal ingrowth of epidermis canalizes the glandular urethra. With newer immunohistochemical techniques and tissue separation and recombination experiments we pro-

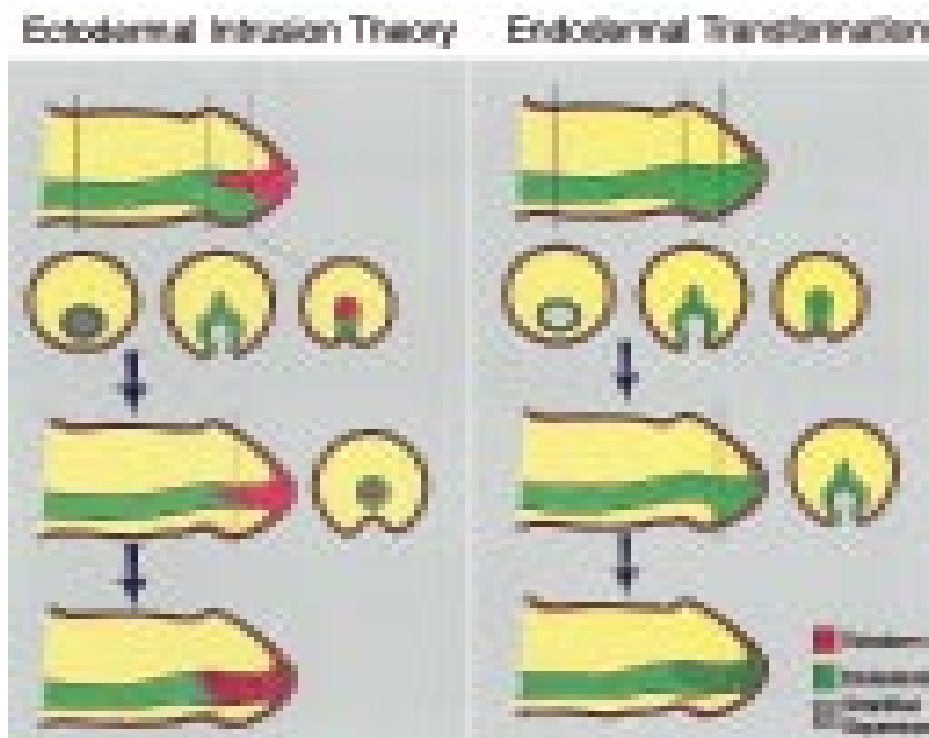


Figure 1 - Theories of human penile urethral development. The ectodermal ingrowth theory as described in most textbooks of embryology postulates that the glandular urethra is formed by ingrowth of epidermis. Our data support the formation of the entire urethra via endodermal differentiation alone (with permission, from ref. 10).

To test the hypothesis that epithelia-mesenchymal interactions are critical for normal penile growth and differentiation an extensive study was performed using the mouse genital tubercle (10). Various epithelial mesenchymal separation experiments were performed to show the importance of epithelial-mesenchymal signaling. When normal signaling was present the growth of the genital tubercle exhib-

ited normal growth and differentiation (defined by the presence of cartilage). In contrast, removal of the developing epithelium [epidermis (skin) and endoderm (urethra)] greatly stunted the growth of the genital tubercle.

Basic work on penile growth has led us to reexamine the embryology of the urethral development (11). The most widely accepted mechanism

posed a new theory to explain the formation of the male distal urethra. Thirty-six human fetal phallic specimens, gestational ages 5-22 weeks, were sectioned and stained immunohistochemically with antibodies raised against different cytokeratins. Evaluation of the sections showed that the urethral plate, an extension of the urogenital sinus, extended to the tip of the phallus and maintained patency and continuity throughout the process of urethral development. The entire urethra, including the glans portion, was formed by dorsal extension and disintegration of the urethral plate combined with ventral growth and fusion of the urethral folds. Sections of the distal glandular urethra showed no evidence of a solid ectodermal ingrowth. Rather, immunostaining results at different ages suggested differentiation of the endodermal urethral plate into a stratified squamous epithelium (11). To determine whether urothelium could be induced to express a stratified squamous phenotype, mouse fetal bladder epithelium was combined with rat fetal genital tubercle mesenchyme and grown under the kidney capsule of athymic mice. The bladder epithelium differentiated into a stratified squamous epithelium. Thus, proper mesenchymal signaling may induce differentiation of urothelium into a stratified squamous epithelium, such as during development of the urethra of the glans penis. Figure-1 is a schematic of the classic theory of ectodermal intrusion contrasted with the new theory of endodermal differentiation supported by our experiments. If we are going to understand the etiology of hypospadias it is critical that we understand normal penile and urethral development.

Endocrine Disrupters

One possible explanation for the worldwide increase in the incidence of hypospadias may be environmental contamination, which could interfere with the normal androgen pathways and normal cellular signaling. In this regard it is well established that humans continually ingest substances with known estrogenic activity such as insecticides utilized in crop production, natural plant estrogens, by-products of plastic production and pharmaceuticals. Indeed, the metal cans used in the food industry are coated inter-

nally with plastic known to contain estrogenic substances. Many of these estrogenic substances find their way ultimately into fresh and seawater in trace amounts, but are bio-accumulated and concentrated in higher organisms of the food chain. For this reason predators at the top of the food chain (large fish, birds, sea mammals and humans) accumulate high levels of estrogenic environmental contaminants. For many species of wild life the consequences for reproduction and health are devastating. For example, the thinning of eggshells in a variety of birds was ultimately traced to the estrogenic activity of insecticides to which the birds were exposed through their diet. Thus, humans and wild animals are constantly exposed to estrogenic compounds known for their ability to disrupt reproduction, so called endocrine disrupters.

Estrogenic contaminants are known to impair penile development in the American alligator (12). Moreover, the potent estrogen, estradiol 17-beta, is known to disrupt penile development in mice even though very little is known about the molecular mechanisms whereby exogenous estrogens perturb penile development (13). In a general sense the normal process of penile development is poorly understood at the cellular and molecular levels. Thus, it is

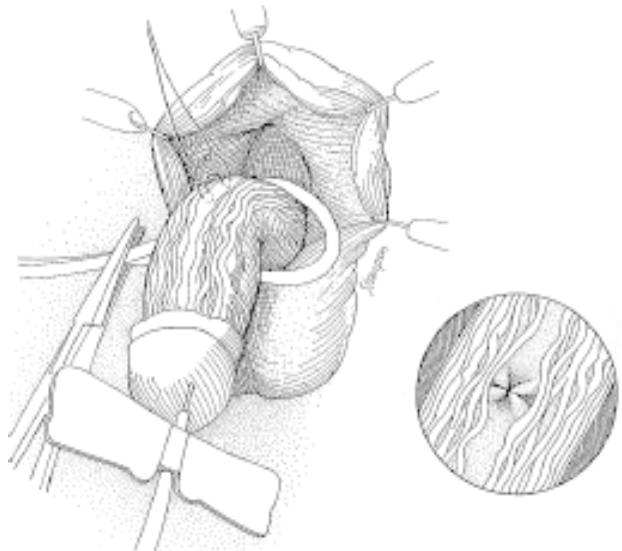


Figure 2 - Penile curvature correction plication suture technique at the 12:00 o'clock position for the correction of ventral curvature. This technique has the theoretical advantage in that it does not injure any nerves or vessels and the sutures are placed in the thickest and hence strongest part of the tunica.

paramount to initiate basic research into the mechanism of normal penile development in concert with studies designed to test the hypothesis that estrogenic compounds can perturb penile development. If it can be established that estrogenic endocrine disrupters are responsible for the increased incidence of hypospadias, preventive steps can be taken to minimize contact with such agents. In the final analysis prevention is the best strategy for this serious medical problem.

ANATOMICAL STUDIES AND RECONSTRUCTIVE IMPLICATIONS

Over the last three years, we have performed careful anatomical studies on genital specimens between the ages of 8 and 33 weeks. In short, speci-

analysis of the male specimens revealed localization of the nerves dorsally not only at the 11 and 1 o'clock position but extending around the tunica to the junction of the corpus spongiosum and corpora cavernosa suggesting that we may be injuring these structures in penile straightening procedures (6,8).

The tunica albuginea showed consistent variations in thickness, with the mid dorsal 12 o'clock position being the thickest followed by the 5 and 7 o'clock periurethral positions. The lack of nerves and the thickness of the tunica at the 12 o'clock position have led to the design of penile straightening procedures by the placement of plication sutures (Figure-2) (6,8).

Analysis of female specimens showed that the normal fetal clitoris consists of two corporal bodies with a midline septum. The ultrastructure of the

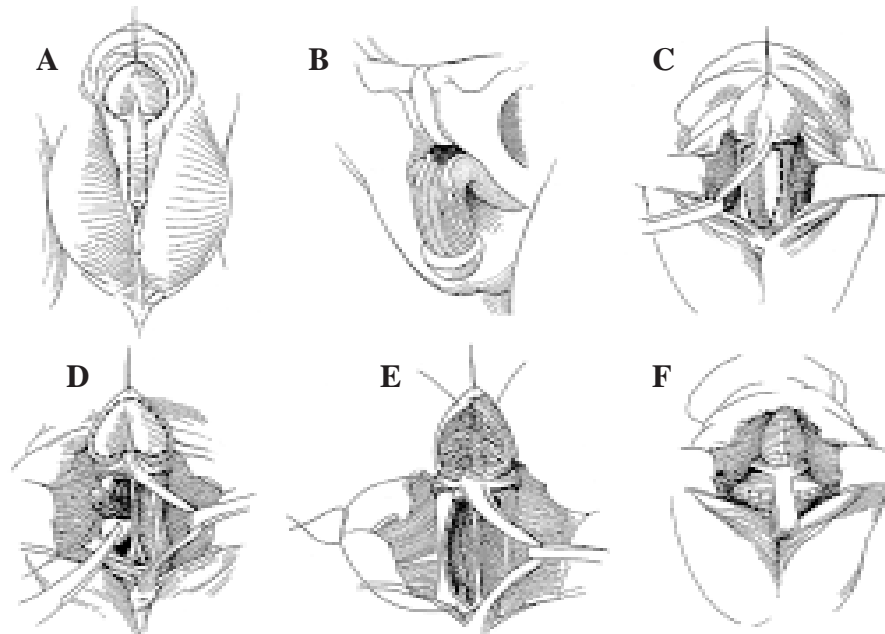


Figure 3 - Schematic of feminizing genitoplasty based on neuroanatomical studies. A)- clitoroplasty incision; B)- schematic representation of nerves based on anatomical studies; C)- mobilization of urethral plate and outline for ventral incision into corporal bodies; D)- reduction of erectile tissue and incision for glans reduction; E)- corporal and glans reduction; F)- reduced glans clitoris with erectile preservation.

mens were serially sectioned and stained for epithelial, smooth muscle and nerve structures using immunocytochemical techniques. Select specimens were reconstructed in 3 dimensions to better understand the relationship between the nerves, corporal bodies and urethral spongiosum using the computer software NIH imaging and Adobe Photoshop® (6). Careful

female corporal bodies is analogous to the male counterpart. The glans clitoris forms a cap on top of the distal end of the corporal bodies. Large bundles of nerves course along the corporal bodies with the greatest density on the dorsal aspect. These anatomical relationships are useful when preserving nerves during feminizing genitoplasty surgery (Figure-3) (7).

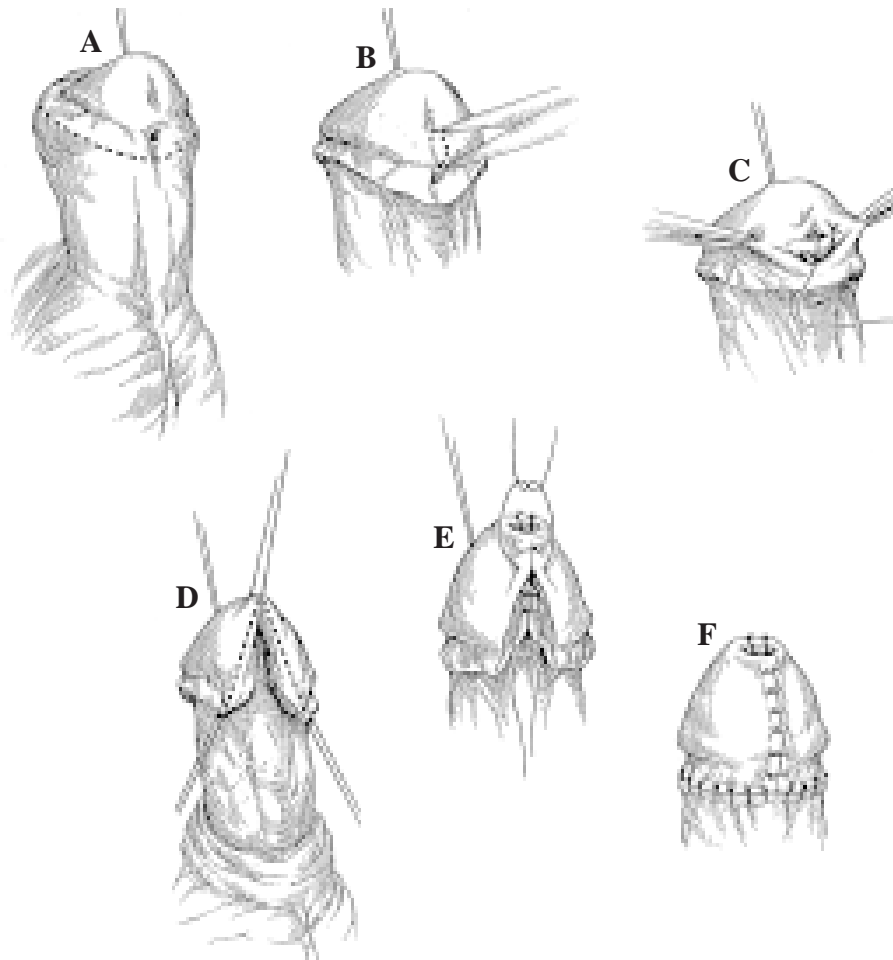


Figure 4 - MAGPI hypospadias technique. A)- shows the initial maneuver of the circumferential subcoronal incision; B) and C)- shows the Heineke-Mikulicz incision and closure of the dorsal meatus after excision of the dorsal web skin bridge; D)- illustrates the most critical step which is exposure of glans mesenchyme, by trimming excess skin illustrated by the dash lines in the figure, and advancing the mobile urethra with the use of a 6-0 chromic suture, or in the case of schematic a skin hook; E)- shows a two layer closure of the glans mesenchyme over the advanced urethra, allowing for a normal appearing glans with excellent support of the urethra; F)- illustrates skin closure with a sleeve approximation of the penile shaft skin. In cases where there is a ventral skin deficiency, a Byer's flap rearrangement with a standard mid-line seems appropriate. (From Hinman F Jr, *Atlas of Pediatric Urologic Surgery*. Philadelphia, WB Saunders Co, pp. 575-578, 1994, used by permission).

Finally, the ultrastructure of hypospadias has revealed that the nerves and corporal bodies have the same anatomical relationship as the normal penis. The most striking difference between the normal penis and the hypospadiac penis is the difference in vascularity. The hypospadiac penis has huge endothelial lined vascular channels filled with red blood cells. In contrast, the normal penis has well defined small capillaries around the urethra and fanning into the glans

(8,14). The anatomy of the normal and hypospadiac penis is relevant to the surgical techniques in respect nerve and vascular preservation.

TREATMENT

The only treatment for hypospadias is surgical repair of the anatomical defect (15-18). In experienced hands the surgery is typically performed

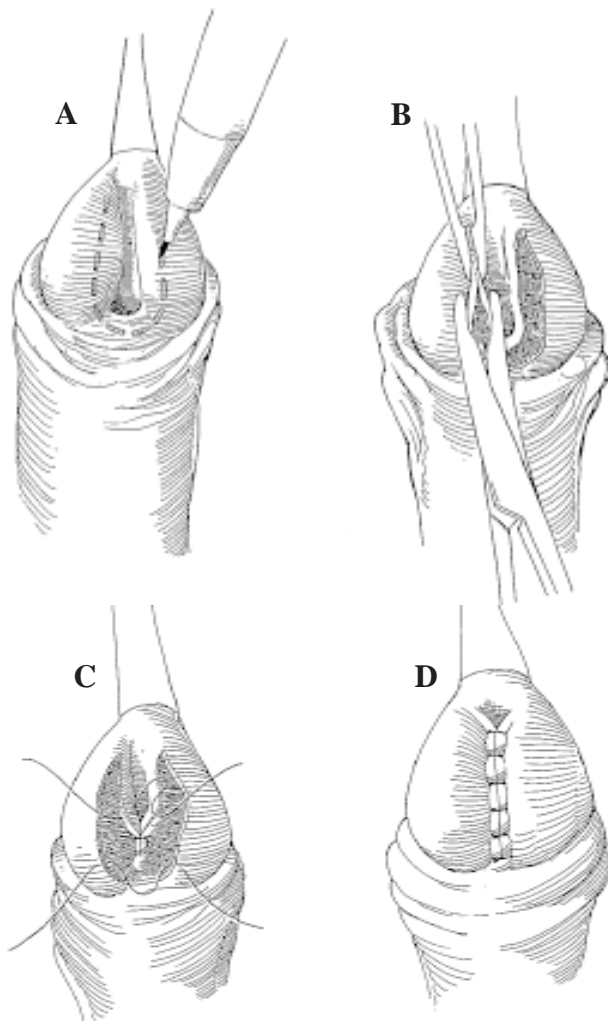


Figure 5 - GAP Hypospadias technique. A)- illustrates the initial incision; B)- shows the exposure of the glans mesenchyme by de-epithelialization of tissue, which is critical for a two-layer glans closure, allowing for good support of the urethroplasty; C)- tubularization of the neourethra followed by glans closure and (Figure D) the completed repair.

as an outpatient procedure with 80-90% of children requiring one operation. Since the surgery is elective, the optimum time as recommended by the American Academy of Pediatric Consensus Panel on genital surgery is between 6 months and 18 months (19).

Anterior Hypospadias

The technique chosen for the repair of anterior hypospadias will depend on the anatomy of

the hypospadiac penis. The most common accepted procedures are the MAGPI (meatal advancement glansplasty), the GAP (glans approximation procedure), the Mathieu or flip-flap and the tubularized incised plate urethroplasty (20-33). We have been most pleased with the results from the MAGPI and GAP procedure, which we present in more detail below. The Mathieu is based on a random flap, which is not as reliable as a vascularized pedicle graft. Long-term complications from meatal stenosis secondary to ischemia have been more common (17).

The MAGPI Technique

The MAGPI technique was devised by Duckett in 1981 (20). This technique will provide outstanding results if appropriate patient selection is followed. The hypospadiac penis that is amenable to the MAGPI is characterized by a dorsal web of tissue within the glans that deflects the urine from either a coronal or a slightly subcoronal meatus. Once the patient is asleep, the urethra itself must have a normal ventral wall, without any thin or atretic urethral spongiosum. The urethra also must be mobile so it can be advanced into the glans (Figure-4).

The GAP Procedure

The GAP procedure is applicable in a small sub-set of patients with anterior hypospadias who

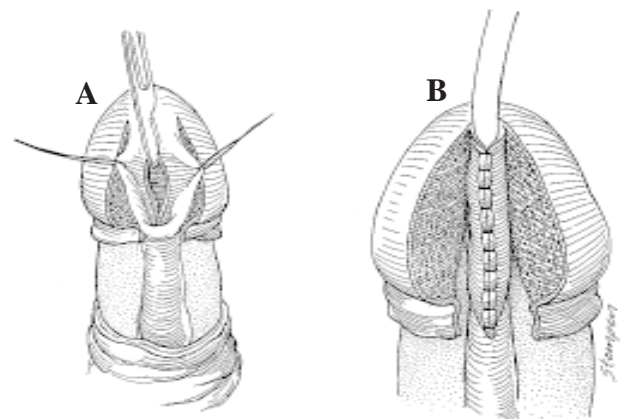


Figure 6 - Tubularized incised plate urethroplasty. A)- note the deep incision in the urethral plate down to corporal tissue; B)- tubularization of neourethral with subsequent glansplasty.

have a wide and deep glandular groove (21). These patients do not have a bridge of glandular tissue that typically deflects the urinary stream, as seen in patients who would be more appropriately treated with the MAGPI procedure. In the GAP procedure, the wide mouth urethra is tubularized primarily over a stent (Figure-5).

more severe hypospadias, a vascularized pedicle flap was performed. Recently the concept of the incision in the urethral plate with subsequent tubularization and secondary healing has been introduced by Snodgrass (Figure-6) (22). Short-term results have been excellent and this procedure is enjoying extensive popularity (25). One appealing

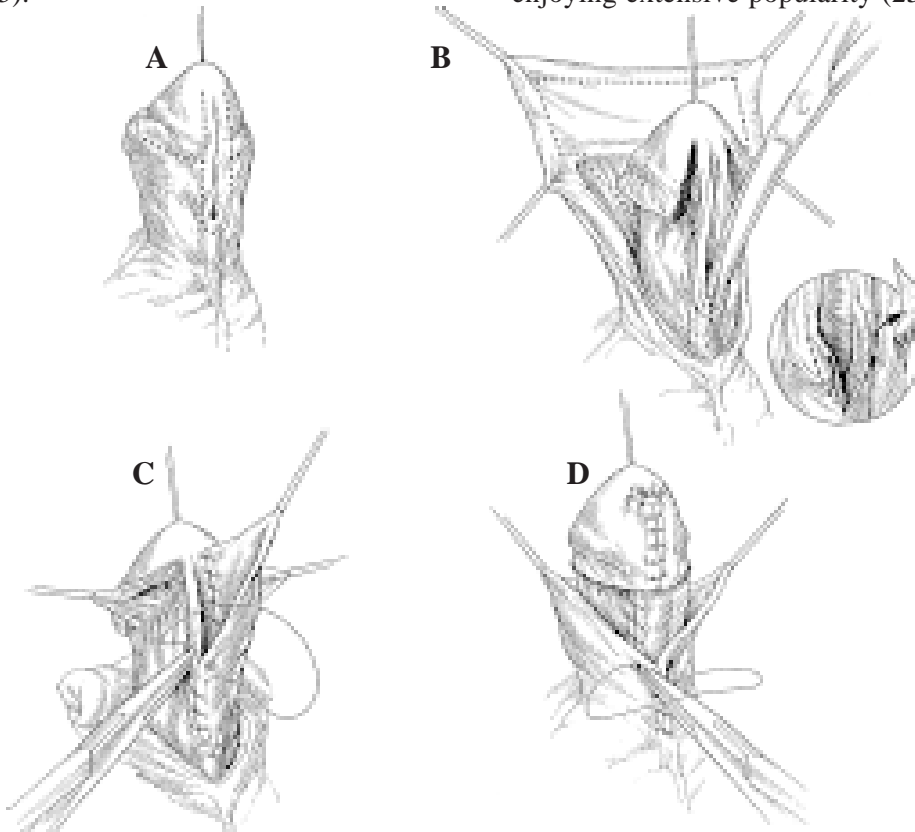


Figure 7 - Onlay island flap hypospadias repair. A)- a U-shaped incision is made around the urethral plate preserving a dorsal urethral strip approximately 8 mm wide; B)- shows take-down of the skin and subcutaneous tissue, as well as outlining the inner prepuce for the onlay island flap. Glans wings are mobilized along the plane of the corporal body and the glans mesenchyme; C)- show preservation of the urethral plate with penile curvature in a case of penoscrotal hypospadias; D)- illustrates suturing of the onlay flap with running 7-0 suture to the urethral plate. The flap is trimmed to obtain a 12 French caliber bougie in a child of one year of age, to prevent the complication of urethral diverticulum, which results from leaving excess tissue. The glans wings are approximated over the new urethra after maturing the meatus and then the skin is closed by a classic Byers flap skin rearrangement.

Tubularized Incised Plate Urethroplasty

Historically, if the urethral groove was not wide enough for tubularization in situ, such as in the GAP or Thiersch Duplay procedure (21,24) then an alternative approach such as the Mathieu or for

aspect is the slit-like meatus, which is created with the dorsal mid-line incision. More recently, this technique has been applied to more posterior forms of hypospadias. Theoretically, there is concern about the possibility of meatal stenosis from scarring as occurs in patients with urethral stricture disease

where direct vision internal urethrotomy often leads to recurrent stricture. In hypospadias, the native virgin tissue with excellent blood supply and large vascular sinuses seems to respond to primary incision and secondary healing without scar (8,14).

Posterior Hypospadias

We have been quite satisfied with the onlay island flap hypospadias technique for the majority of penile shaft and more severe cases of hypospadias (Figure-7). The onlay island flap has withstood the test of time with excellent long-term results (15,17). Preservation of the urethral plate in the onlay island flap has essentially eliminated proximal anastomotic strictures and has reduced the incidence of fistula formation. When necessary penile curvature is corrected by dorsal plication (Figure-2)(8).

Recent reports have summarized standard techniques and introduced subtle variations (26-29). Occasionally extensive surgery is necessary and in some cases multiple operations leave the unfortunate child with a suboptimal result, the patient then being classified as a "hypospadias cripple". For very severe hypospadias, the prepuce can be designed as a horseshoe style to bridge extensive gaps (30).

CONCLUSION

In summary, in the last twenty years there has been an incredible evolution in the surgical treatment of hypospadias. Optical magnification, delicate tissue handling and fine sutures have greatly benefited patients and families with this congenital anomaly. The next step is to begin to understand the etiology of hypospadias. This is especially germane if the incidence of hypospadias is truly doubling. A multidisciplinary effort is warranted in the areas of androgen metabolism and epithelial-mesenchymal signaling based on the hypothesis that endocrine disrupters may account for the documented increase incidence of hypospadias. Through a better understanding of normal penile growth and urethral differentiation new strategies of prevention and treatment can be developed.

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