INTRODUCTION

Vesicoureteral Reflux (VUR) is defined as the retrograde flow of urine from the bladder back into the ureters and renal collecting system due to a failure of the ureterovesical valve mechanism. Vesicoureteral reflux is diagnosed in approximately 1% of children and promotes pyelonephritis ***(Berisha et al., 2014)***.

Primary VUR is presented in 30-50% of children with urinary tract infection (UTI), and in approximately 10% of patients with prenatally diagnosed hydronephrosis. The condition occurs 10 times more frequently in white children than in black children, and is more prevalent in male newborns than in female newborns ***(Novak et al., 2009).***

The grading system is based upon the extent of retrograde filling and dilatation of the ureter, the renal pelvis and the calyces on a VCUG.

- ***Grade I***: Reflux does not reach the renal pelvis
- ***Grade II***: Reflux reaches the renal pelvis
- ***Grade III***: Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system;

- ***Grade IV***: Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible.

- ***Grade V***: Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible ***(Chertin and Kocherov, 2010).***

For grades I and II VUR long-term prophylaxis to prevent urinary tract infection (UTI) is generally recommended as initial therapy, while waiting for spontaneous resolution ***(Nicola et al., 2004).***

American Urology association (AUA) Reflux Guide lines reported 90% resolution rate and a 80% resolution rate for grade I &II, respectively at 5 years independent of age at diagnosis or whether VUR was unilateral or bilateral. In contrast, in children grade III VUR diagnosed at 6 years of age or older, resolution rate was only 10% ***(Routh et al., 2006).***

For many years, open surgery was standard treatment for high-grade vesicoureteral reflux. Although ureteral reimplantation is effective, this operation has many complication ***(Chertin and Puri, 2003)***.

Matouschek (1981) first described the injection of polytetrafluo-roethylene (PTFE) paste at the ureteral orifice to correct VUR ***(Khoury and Bägli, 2012).***

Endoscopic treatment for vesicoureteral reflux (VUR) has become an established alternative to long-term antibiotic prophylaxis and ureteral reimplantation ***(Berisha et al., 2014).***

Several agents have been used for endoscopic correction of VUR. These materials can be classified as particulate and degradable or autologous and non-autologous ***(Oberson et al., 2007).***

In 1999, Diamond and Caldamone reported preliminary results of endoscopic injection of **autologous chondrocytes** to correct VUR in children. Because chondrocytes possess the ability to form viable cartilage, they have good potential as a stable tissue augmenting substance ***(Caldamone and Diamond, 2001).***

Non-autologous Materials include Polytetra-fluoroethylene (PTFE), Cross-linked bovine collagen, Polydimethylsiloxane, Dextranomer hyaluronic copolymer (Deflux), Coaptite, while Autologous Materials include Chondrocytes, Fat, Collagen, Muscle ***(Khoury and Bägli, 2012).***

Dextranomer/Hyaluronic Acid Copolymer (Dx/HA) copolymer (Deflux) is the most common tissue augmenting substance used for injection. Deflux is biodegradable, is non immunogenic, and has no potential for malignant transformation ***(Chertin et al., 2011).***

Aim of the Work

The aim of this study is to evaluate the endoscopic management of primary vesicoureteric reflux in children by injection of Dextranomer/ Hyaluronic Acid Copolymer.

Chapter 1

EMBRYOLOGY OF THE VESICOURETERAL JUNCTION AND TRIGONE

Origin of ureter

By day 33 of gestation, the embryonic ureter (metanephric duct) buds from the mesonephric or wolffian duct ***(Sadler, 2000)***.

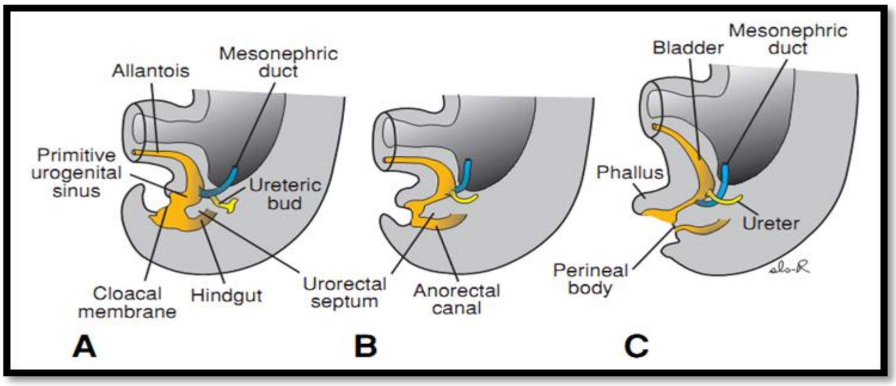

Figure (1): Divisions of the cloaca into the urogenital sinus and anorectal canal. The mesonephric duct is gradually absorbed into the wall of the urogenital sinus, and the ureters enter separately. [A- At the end of the fifth week B- 7 weeks. C- 8 weeks] ***(Sadler, 2000)***.

Origin of trigon and developing an antireflux mechanism

The common excretory ducts (the portion of mesonephric ducts distal to the origin of ureteric buds) dilate and become absorbed into the urogenital sinus. The right and left common excretory ducts fuse in the midline as a triangular area, forming the primitive trigone ***(Sadler, 2000)***.

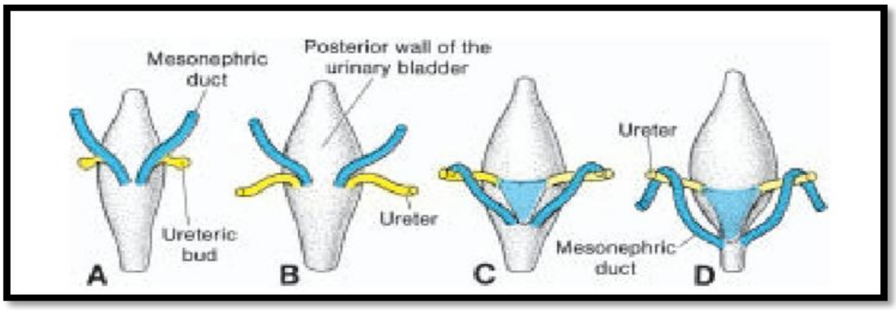

Figure (2): Dorsal views of the bladder showing the relation of the ureters and mesonephric ducts during development. (A)- Initially the ureters are formed by an outgrowth of the mesonephric duct . (B – D) with time they assume a separate entrance into the urinary bladder . Note the trigone of the bladder formed by incorporation of the mesonephric ducts (C and D) ***(Khoury and Bägli, 2007).***

Abnormalities

If the ureteral bud reaches the urogenital sinus too soon (believed to be due to early budding), over-rotation draws it high and lateral in the bladder wall and leads to inadequate incorporation, insufficient intramural length in the bladder wall that leads to 1ry vesicoureteral reflux ***(Davies, 2001).***

If the ureteral bud reaches the urogenital sinus too late (because of budding late), insufficient rotation occurs and results in an ectopic ureter that is drawn distally and medially ***(Khoury and Bägli, 2016).***

The more distant the site of origin of the bud from the wolffian duct, the more severe the degree of reflux ***(Capozza et al., 2007)***.

According to the Weigert-Meyer rule, an abnormally lateral lower pole ureteric orifice may result from a ureteric bud arising too low on the nephric duct, resulting in premature incorporation and migration within the developing bladder. In such a ureteric orifice, vesicoureteral reflux is more likely to occur because of an inadequate intramural tunnel ***(Khoury and Bägli, 2016).***

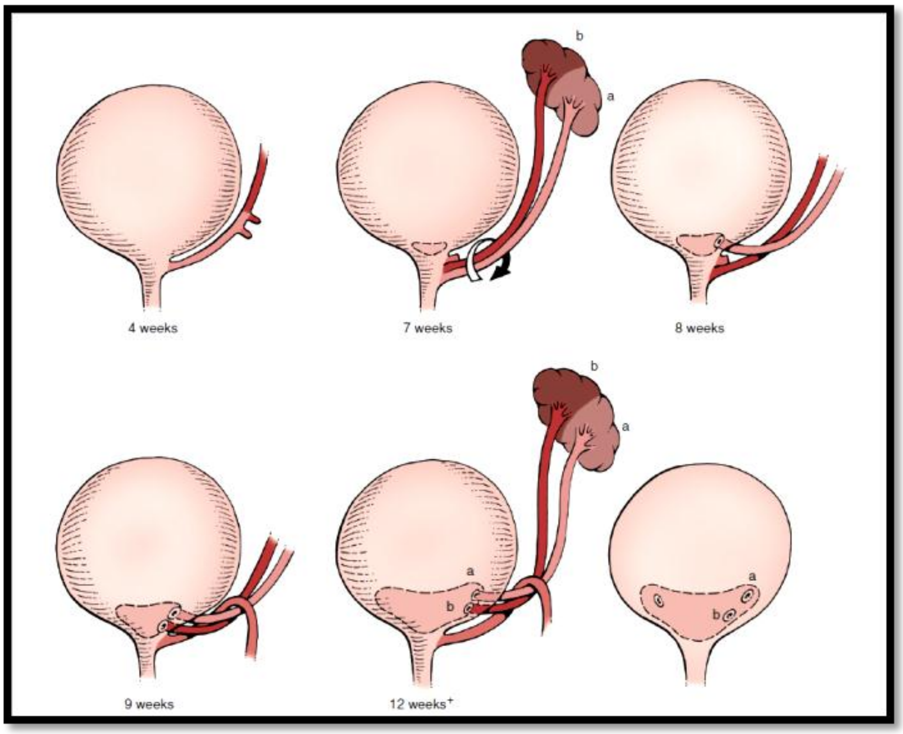

Figure (3): The Weigert-Meyer rule. The upper pole ureter and the lower pole ureter rotate on their long axes to yield an upper pole orifice *(b)* that is medial and caudal to the lower pole orifice *(a)* ***(Khoury and Bägli, 2012).***

In contrast, an abnormally caudal upper pole ureteric orifice may result from a ureteric bud arising too high on the nephric duct. It may drain at the bladder neck and verumontanum or remain connected to the nephric (wolffian) duct derivatives such as the vas deferens. In females, the ectopic upper pole ureter may insert into the remnants of the nephric ducts (such as a Gärtner's duct cyst) or vaginal vestibule ***(Belman, 2008)***.

Chapter 2

ANATOMY OF URETER

The distal portion of the ureter is divided into the juxtavesical ureter and the terminal ureter. The terminal ureter subsequently separates into the intramural and submucosal components ***(MacLennan, 2012)***.

The ureter is enclosed in a loose, ill-defined sheath beneath the peritoneum. Proximally, the ureteral sheath and the ureteral adventitia become continuous with the renal pelvis. Distally, the sheath and ureteral adventitia join to form the Waldeyer sheath, which extends into the bladder wall as a portion of the deep trigone ***(Khoury and Bägli, 2016).***

The ureter is composed of three layers: adventitia, a muscular coat, and mucosa. The adventitia consists of longitudinally running collagen fibers. The adventitia along with the outer ureteral sheath is loosely attached to the underlying muscularis, allowing for free peristaltic activity ***(MacLennan, 2012)***.

The muscularis comprises smooth muscle cells interspersed with collagen fibers. The muscle bundles are arranged in three distinct layers: inner longitudinal, middle circular, and outer longitudinal this configuration changes into longitudinally oriented muscle fibers with sparse collagen as the ureter enters the bladder and intramural region., roof fibers swing to either sides to join the floor fibers and spread out to join equivalent muscle bundles from the other ureter and continue caudally to form superficial trigone (uretro-trigonal complex) ***(Khoury and Bägli, 2016).***

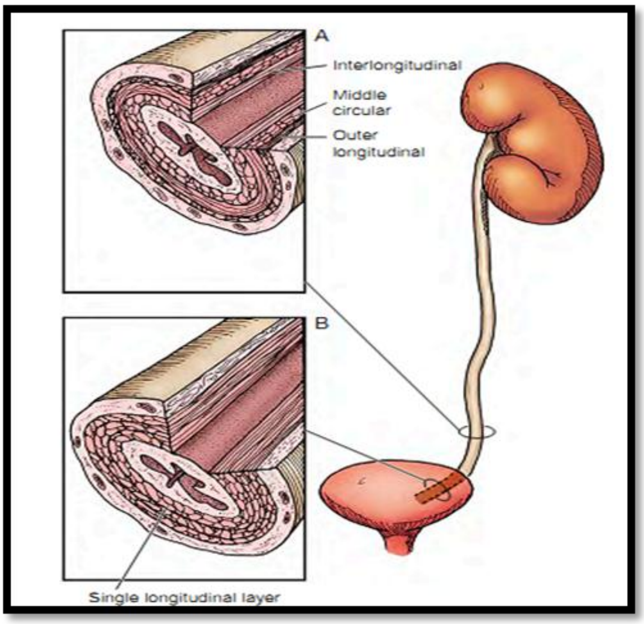

Figure (4): anatomy of ureter (A) Cross section of distal ureter shows that the muscularis comprises three layers of smooth muscle bundles the inter- longitudinal, middle circular, and outer longitudinal.**(B)** Cross section of the intramural ureter shows only the longitudinally oriented muscle fibers ***(Chertin and Puri, 2003)***.

Anatomy of trigone

The superficial trigone passes over bladder neck to end at vermontanum in male and just at external urethral meatus in female ***(Khoury and Bägli, 2016).***

Beginning at point 2-3 cm above the bladder, an external layer of longitudinal smooth muscle fibers forming muscular sheath (waldeyer`s sheath), which is connected by detrusor fibers of vesical wall. As muscular sheath entering bladder wall, its roof fibers diverge to join floor fiber and spread out joining those of contralateral ureter forming deep trigone which ends at bladder neck ***(Drake et al., 2005).***

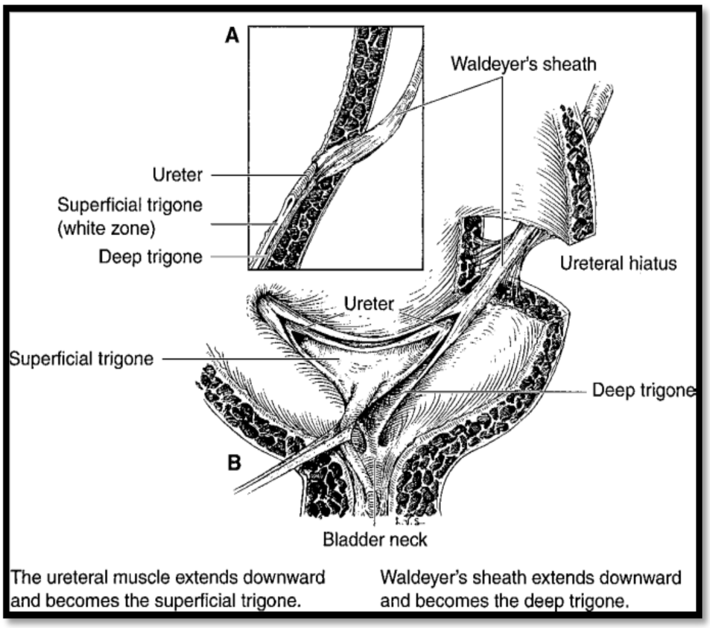

Figure (5): Normal ureterotrigonal complex. **(A)** Side view of ureterovesical junction. **(B)** Configuration of superficial and deep trigon ***(Drake et al., 2005).***

Functional competence of vesico-ureteral junction

The ureter represents a dynamic conduit that adequately propels the urine in a bolus fashion, antegrade, by neuromuscular propagation of peristaltic activity ***(Khoury and Bagli, 2016).***

The UVJ is structurally and functionally adapted to allow the intermittent passage of ureteral urine and to prevent the reflux of bladder urine. To achieve these functions, the ureter enters the bladder with an oblique intramural passage, which extends submucosally to open onto the trigone ***(Chertin and Puri, 2003)***.

Paquin's early dissections of the UVJ in children revealed an approximate 5:1 ratio of tunnel length to ureteral diameter in nonrefluxing junctions versus a 1.4:1 ratio in refluxing UVJs ***(Khoury and Bägli, 2016).***

Table (1): Mean Ureteral Tunnel Length and Diameter in Normal Children ***(Khoury and Bägli, 2016).***

Age (yr)	Intravesical Ureteral Length	Submucosal Ureteral Length	Ureteral Diameter at the Uretero-vesical Junction
1-3	7 mm	3 mm	1.4 mm
3-6	7 mm	3 mm	1.7 mm
6-9	9 mm	4 mm	2.0 mm
9-12	12 mm	6 mm	1.9 mm

The natural tonus of the ureteral muscles and uretero-trigonal complex maintain an active closure of the intravesical ureter except during the efflux of urine ***(Chertin and Puri, 2003)***.

The longitudinal ureteral muscles intermingle with those of the superficial trigone and the contralateral ureter so that contraction elongates the submucosal tunnel. The adventitia fuses with a fibrous sheath (Waldeyer) circumferentially, allowing the intramural ureter to move within the hiatus during bladder filling. As the bladder fills and becomes distended, there is progressive obliquity of the intravesical ureter; the trigone is progressively stretched, increasing resistance in the intravesical ureter and causing increased pressure within the distal end of the ureter ***(Oberson et al., 2007).***

During micturition, when the trigone is stimulated, the intravesical ureter is pulled downward, and the ureteral walls are compressed against the supporting vesical wall as a passive reinforcement of the valvular mechnism. These actions anchor the ureter, retaining its correct configuration and preventing lateral displacement of the ureteral orifice. The mechanism requires a complex of muscular components that includes ureteral and vesical muscle bundles and an elaborate neural influence ***(Drake et al., 2005).***

Chapter 3

EPIDEMIOLOGY AND ETIOLOGY OF VESICO-URETERAL REFLUX

- ***Incidence and Prevelance***

The incidence of VUR is 0.4–1.8% in the general pediatric population ***(Capozza et al., 2007).***

Prevalence of VUR was estimated to be 19%, with high-grade reflux being present in more than half the refluxing group ***(Barai et al., 2004)***.

In asymptomatic infants monitored for antenatal hydronephrosis, the prevalence of reflux ranged from 15% in infants with absent or mild hydronephrosis on postnatal ultrasound ***(Phan et al., 2003)***.

The tendency for VUR to resolve spontaneously on the one hand or persist beyond its natural resolution rate due to abnormal bladder dynamics makes it difficult to confidently generalize the true prevalence of reflux from a given population ***(Khoury and Bägli, 2012).***

- ***Gender***

Gender analysis shows that VUR occurs in girls older than the age of 1 y, four to five times more often than in boys of the same age ***(Merguerian et al., 2004).***

However, high-grade neonatal VUR is strongly associated with male gender, possibly because of increased outlet resistance ***(Chandra and Maddix, 2005).***

- ***Age***

The natural history of reflux involves spontaneous resolution over time, so the primary reflux would be prevalent in infant compared with older children **table (2)** ***(Smellie, 1999).***

Table (2): Relation of incidence of reflux to age ***(Khoury and Bägli, 2012).***

AGE (yr)	INCIDENCE (%)
• <1	• 70
• 4	• 25
• 12	• 15
• Adult	• 5.2

- ***Familial and genetic aspects***

There is evidence for genetic heterogeneity of VUR, suggesting that the most likely mode of inheritance for VUR is dominant ***(Khoury and Bägli, 2012).***

Greenfield and Hallowell performed a review of studies that included routine cystogram screening of the siblings of affected VUR cases. The mean incidence of VUR in siblings was greater than the rate in the general population at 32% (570 of 1768 individuals), with the majority having low grades of reflux ***(Greenfield and Hallowell, 2002).***