

Vesicoureteric Reflux in Children

Essay

*Submitted for Partial Fulfillment of Master Degree in
Urology*

Presented By

WASEEM NAGUIB NAZEER

M.B., B.Ch

(South Valley University)

Under Supervision of

Prof. Mohammed Amin Elbaz

Professor of Urology

Faculty of Medicine - Ain Shams University

Dr. Mahmoud Ahmed Mahmoud

Lecturer of Urology

Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

2010

Introduction

Vesicoureteric reflux (VUR) is the retrograde flow of urine from the bladder into the ureters. It is the most common urological anomaly in children, and a major cause of end-stage renal failure and hypertension in both children and adults (**Kelly et al, 2007**).

In 1893, Pozzi was first to observe reflux in humans when he noted urine flow from the cut end of the distal ureters while he was performing nephrectomy (**Ross, 2001**).

Vesicoureteric reflux is a common finding in pediatric practice that occurs in about 1% of children and is often familial, with several genetic loci probably involved. The majority of low-grade cases have a tendency to resolve spontaneously during childhood. However, VUR has been identified as a risk factor for the development of urinary tract infections (UTI) and is present in one third of young children presenting with this problem. In addition, some children with high-grade VUR have already renal lesions before the advent of any UTI (**Ismaili et al, 2006**).

Hydronephrosis is the most common genitourinary anomaly as detected on obstetric ultrasonography and the incidence of associated vesicoureteral reflux is around 10-12%. Children with antenatal hydronephrosis (AHN) should undergo an ultrasound within the first month of life and further management should be decided on the basis of the individual case. Children with *persistent* moderate to severe AHN should

undergo a voiding cystourethrography (VCUG) and a functional study (*Ansari et al, 2009*).

A study was done for evaluation the efficacy of dimercaptosuccinic acid (DMSA) scan and abdominal ultrasound (US) in comparison with VCUG in detection of vesicoureteral reflux (VUR) in children below the age of 2 years after their first febrile urinary tract infection (UTI). VUR was detected in 30.4% of cases (by VCUG). The detection rate of VUR by US was 41.7% and 86% in the low (I, II) and high grade (III~IV) groups, respectively. Detection rate of VUR by DMSA scan was 37.5% and 88.4% in the low and high grade groups, respectively. Combining US and DMSA scan, the detection rate of high grade VUR was 95.3% and that of low grade was 62.5%. Most of the low grade VURs with *normal* DMSA and US scans resolved or were downgraded without complications. (*Lee et al, 2009*).

The risk of developing renal scars is higher in the first years of life, mostly when the patient has vesicoureteral reflux, for that reason is necessary to identify this reflux as early as possible. The presentation of a urinary tract infection in the neonatal period was associated with vesicoureteral reflux in 20.9% of the cases, most frequently caused by primary vesicoureteral reflux and the dilatant degrees. There was no significant difference by gender (*Alvarez et al, 2009*).

The current management of vesicoureteral reflux (VUR) focuses on the prevention of urinary tract infections (UTI), with curative surgery being limited to those children that fail conservative measures. This is based on the assumption that UTIs are preventable with the use of prophylactic antibiotics, leading to reduction of renal scarring, and the possibility that VUR in children can resolve spontaneously (**Mathews et al, 2009**).

Endoscopic treatment for vesicoureteral reflux has become an established alternative to long-term antibiotic prophylaxis and ureteral reimplantation. Endoscopic treatment with dextranomer/hyaluronic acid is safe and highly effective for eradicating high grade vesicoureteral reflux in infants. Early intervention in infants with high grade reflux may change its natural history and protect against renal scarring (**Puri et al, 2007**).

During a 5-year period after dextranomer/hyaluronic acid was introduced for endoscopic therapy the number of children newly diagnosed with vesicoureteral reflux treated with early antireflux surgery increased primarily due to increased use of endoscopy. This finding suggests that despite the lack of evidence of benefit, endoscopy is increasingly viewed as first line therapy for reflux (**Nelson et al, 2009**).

Aim of the Work

The aim of this work is to discuss vesicoureteric reflux in children and to highlight recent methods of diagnosis, evaluation and management.

Epidemiology and Demographics

Primary vesicoureteral reflux (VUR) has long been recognized as a major child and public health problem, affecting approximately 1% to 2% of the pediatric population (*Hayn et al, 2008*).

- **Gender**

Among children younger than 18, the annual reflux related inpatient hospitalization rates was stable between 1994 and 2000 at 6.4–7.0 per 100,000 children. The girl-to-boy ratio was relatively constant at 3:1 (*Miller et al, 2009*).

Similarly, Silva and colleagues reported in their study that included large number of patients with VUR that 28.3% of patients were boys and 71.7% of them were girls. Boys showed a more severe pattern while girls had a greater risk of dysfunctional voiding and recurrent UTI (*Silva et al, 2006*).

Primary vesicoureteral reflux is a common genetically determined condition that is associated with varying degrees of renal damage and represents one of the main causes of chronic renal failure (CRF) in children. The damage can be explained by two mechanisms, which often lead to co-existing renal lesions whose prevalence differs between sexes. The first is congenital renal hypodysplasia, which has very often been found in *male* newborns with severe VUR diagnosed on the basis of fetal ultrasound abnormalities. The second is acquired

segmental scarring as a result of urinary tract infections which has been mainly documented in female children affected by mild/moderate reflux and recurrent UTIs (*Marra et al, 2004*).

- **Race**

VUR has low incidence among black children. They are a third as likely as white ones to have VUR. Furthermore, there is no black girl has high grade reflux (*Chand, 2003*).

- **Age**

Because the natural history of reflux involves spontaneous resolution over time, it is evident that reflux would be less prevalent in older children than in infants. Even in the presence of infection or asymptomatic bacteruria, reflux is more common in younger patients (*Smellie, 1991*).

- **Reflux and UTI**

According to various published estimates, VUR is present in 29%–50% of children with urinary tract infection (UTI) and in approximately 10% of infants with antenatal hydronephrosis (*Silva et al, 2006*).

A study showed that the incidence of VUR of any grade after first febrile UTI in 699 children aged 2 month to 2 years was 29.5% and high-grade VUR was present in 119 children (17%) (*Lee et al, 2009*).

- **Occult vesicoureteric reflux "PIC-VUR" & febrile UTIs**

The incidence of "occult" vesicoureteral reflux in children who experience recurrent febrile UTIs without vesicoureteral reflux on standard cystography is 100% by PIC cystography (Positioning the Instillation of Contrast at the ureteral orifice) (*Rubenstein et al, 2003*).

- **Antenatal hydronephrosis**

Fetal hydronephrosis is the most common anomaly detected on antenatal ultrasound examination and the most common underlying conditions are ureteropelvic junction obstruction and vesicoureteral reflux (*Estrada, 2008*).

In patients with a history of prenatal hydronephrosis who have postnatally persistent grade II hydronephrosis; VUR is found in 28% of cases (*Estrada et al, 2009*).

- **Familial reflux and duplex system**

Duplication of the ureter and renal pelvis is the most common upper urinary tract anomaly in childhood with a reported incidence of 0.8%. Familial nature of vesicoureteral reflux is well recognized with a prevalence of 27-51% in siblings of children with VUR and 66% rate of VUR in offsprings of parents with previously diagnosed VUR. VUR is the most common abnormality associated with renal duplex

system. Patients with duplex systems have a significantly higher grade of VUR than patients without duplex systems. Duplex collecting systems are associated with VUR in (7.6%) patients. Duplex system is coexistent with reflux more in families having only boys affected (15%) than in families having only girls affected (6%) and also than families having both boys and girls affected (6.4%) (*Hunziker,2010*).

- **VUR and posterior urethral valves (PUVs)**

Reflux is the major cause of postnatal renal damage in posterior urethral valves (PUV), and persistent reflux is associated with bad outcome. Priti and colleagues in 2004 reported in their study that VUR was present in 60% of the patients of PUV, being unilateral in 41.7% of cases (*Priti et al, 2004*).

- **Ureteropelvic junction (UPJ) obstruction and VUR**

About 14% of cases of UPJ obstruction undergoing pyeloplasty have VUR. In cases associated with low grades of reflux spontaneous resolution occurs after pyeloplasty. The UPJ in these cases may be primary ureteropelvic junction obstruction, ureteropelvic junction obstruction secondary to high grade reflux, and pseudo-ureteropelvic junction obstruction. In cases of *primary* UPJ with VUR, pyeloplasty should be the initial procedure with use of a nephrostomy tube or Foley catheter postoperatively. In case of secondary UPJ

with VUR the obstructive uropathy should be treated initially, since primary ureteral reimplantation may provoke acute ureteropelvic junction decompensation. Pseudo-ureteropelvic junction obstruction is suggested when pelvic dilatation on the voiding cystourethrogram suggests obstruction but drainage films or antegrade studies document good drainage. The recognition of pseudo-ureteropelvic junction obstruction is important to avoid surgery on an ureteropelvic junction that is not obstructed. Primary correction of the reflux is appropriate. However, it must be recalled that a fixed kink may rarely develop later leading to true secondary ureteropelvic junction obstruction, which will require surgical correction. It is recommended that a voiding cystourethrogram be part of the routine evaluation of children with suspected ureteropelvic junction obstruction (*Hollowell et al, 1989*).

- **VUR and end-stage renal disease (ESRD)**

Chronic kidney disease (CRD) is classified into five stages according to the glomerular filtration rate GFR. The fifth stage in which the GFR is less than 15 ml /min /1.73 m² body surface area is the end stage renal disease ESRD. Renal hypodysplasia with or without urological malformations accounts for as many as 57.6% of all cases of ESRD, whereas glomerular disease is a much less important cause (6.8%). Hypodysplasia associated with primary vesicoureteral reflux alone accounted for as many as 25.8% of the cases of ESRD

and proved to be the **first** single cause of childhood and adolescent CRF (*Ardissino et al, 2003*).

- **VUR and pregnancy**

It was reported that pyelonephritis occurs during pregnancy in 3 of 8 women with reflux, but only 2 of 33 in those without reflux (*Martinell et al, 1990*).

The published studies shows that women with VUR that is not associated with renal scarring have no increase in the incidence of gestational hypertension, pre-eclampsia or fetal morbidity. However, women with VUR and normal kidneys do have higher incidence of urinary tract infection during pregnancy, which is not modified by ureteric reimplantation. Renal scarring is the primary risk factor for morbidity during pregnancy and this risk is independent of the presence or absence of VUR at the time of pregnancy (*Hollowell, 2008*).

Functional Anatomy of the Vesicoureteric Junction

The vesicoureteric junction (UVJ) represents an important area between the low pressure of the upper urinary tract and the variable pressure of the lower urinary tract. UVJ is the region that is most important for preventing VUR (*Radmayr et al, 2005*).

Embryology

Cloaca is the expanded lower end of hindgut into which the mesonephric ducts and embryonic ureters drain. Between the fourth and sixth weeks of gestation, the cloaca is subdivided by the descent of the urorectal septum towards the perineum and by lateral ingrowth of the folds of Rathke. The effect is to compartmentalise the cloaca into the urogenital canal anteriorly and the anorectal canal posteriorly. While the bladder is taking shape in the upper portion of the urogenital canal, the distal ureter and mesonephric duct begin to separate (*Thomas, 2008*).

Two events proceed simultaneously to govern the ultimate position and integrity of the UVJ. At one point, the embryonic ureter buds from the mesonephric or wolffian duct to define the metanephric duct or early fetal ureter. The wolffian duct (early vas deferens) and early ureter can be thought of as forming the two upper arms of a “Y,” with the distal mesonephric duct being the stem of the “Y” [Fig.1].

While budding is occurring, the distal right and left mesonephric duct are being drawn and incorporated into the region of the urogenital sinus (UGS) forming the primitive trigone of the bladder. Incorporation continues until the entire stem is absorbed, with the two arms of the “Y” left to enter the bladder separately: one as the ureter and the other as the vas and ejaculatory duct in the male prostatic urethra or the vestigial Gartner duct in the female vagina. The two arms of the “Y” also rotate relative to each other once they contact the UGS/bladder wall such that the ureteral orifice is located proximal to the ejaculatory duct orifice. If the ureteral bud reaches the UGS 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, and reflux (*Mackie et al, 1975*).

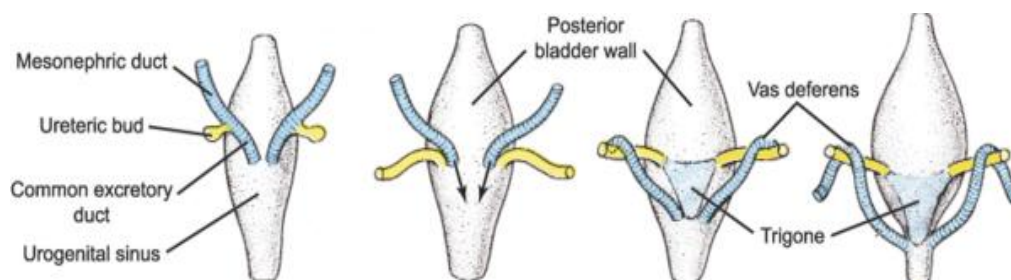


Fig. (1). Incorporation of the mesonephric ducts and ureteric buds into the bladder wall. Between the 4th and 6th weeks, common excretory ducts, the terminal portion of the mesonephric ducts caudal to the ureteric bud formation, exstrophy into the posterior wall of the developing bladder. The triangular region of exstrophied mesonephric ducts forms the trigone of the bladder. This process brings the ureteric bud openings into the bladder wall, while the mesonephric duct openings are carried inferiorly to the level of pelvic urethra (*Park, 2007*).

The phenomenon of VUR represents a balance of several factors. Abnormality in any of these factors alone or in combination will allow or cause retrograde flow of urine from the bladder up the ureter and ultimately to the renal pelvis and tubules. These factors include functional integrity of the ureter, anatomic composition of the UVJ, and functional compliance of the bladder. First, for purposes of reflux prevention, the ureter represents a dynamic conduit that adequately propels the urine presented to it in a bolus fashion, antegrade, by neuromuscular propagation of peristaltic activity. In so doing, reflux is actively opposed. Moreover, if reflux were to occur, depending on its degree and timing, antegrade flow might be expected to keep refluxing urine from reaching the renal pelvis. The second component is the anatomic design of the UVJ. At the heart of this unique mechanism lies an intramural portion of ureter that travels within the detrusor muscle as it traverses the bladder wall (*Khoury and Bagli, 2007*).

- **Microscopic anatomy**

- A. The mesodermal component**

It arises from the Wolffian duct and is made up of 2 parts that are innervated by the sympathetic nervous system:

- 1. The ureter & the superficial trigone**

The smooth musculature of the renal calyces, pelvis, and extravesical ureter is composed of helically oriented fibers that

allow for peristaltic activity. As these fibers approach the vesical wall, they are reoriented into the longitudinal plane. The ureter passes obliquely through the vesical wall; the intravesical ureteral segment is thus composed of longitudinal muscle fibers only and therefore cannot undergo peristalsis. As these smooth-muscle fibers approach the ureteral orifice, those that form the roof of the ureter swing to either side to join those that form its floor. They then spread out and join equivalent muscle bundles from the other ureter and also continue caudally, thus forming the superficial trigone. The trigone passes over the neck of the bladder, ending at the verumontanum in the male and just inside the external urethral meatus in the female. Thus, the ureterotrigoanal complex is one structure. Above the ureteral orifice, it is tubular; below that point, it is flat (*Tanagho and Nguyen, 2008*).

2. Waldeyer's sheath & the trigone

Waldeyer's sheath is found in the juxtavesical segment of the ureter forming an encircling layer around the lowermost 1.5 to 3 cm [Fig. 2 a&b], and histologically it is seen to consist of fibromuscular tissue. As the sheath is traced upwards the amount of muscle gradually decreases, and at its upper limit it consists only of fibrous tissue that has become continuous with the adventitia of the ureter. Dissection of the intravesical part shows that the sheath follows the ureter through the ureteric canal again forming a complete encircling fibromuscular layer around the ureter. At about the level of the junction between the
