



HANNA ROIHUVUO-LESKINEN

Urogenital Problems in Adults  
Following Childhood Vesico-ureteral Reflux



ACADEMIC DISSERTATION

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UNIVERSITY OF TAMPERE

HANNA ROIHUVUO-LESKINEN

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## List of original publications

- (1) Roihuvuo-Leskinen H, Koskimäki JE, Tammela TL, Lahdes-Vasama TT. Urine flow curve shapes in adults with earlier vesicoureteral reflux. *Eur Urol* 2008;54(1):188-195.
- (2) Lahdes-Vasama TT, Roihuvuo-Leskinen H, Koskimäki JE, Tammela TL. Urodynamical findings on women with voiding problems and earlier vesico-ureteral reflux. *Neurourol Urodyn* 2009;28(8):1015-1021.
- (3) Roihuvuo-Leskinen H, Lahdes-Vasama T, Niskanen K, Rönholm K. The association of adult kidney size with childhood vesicoureteral reflux. *Pediatric Nephrology* 2013;28(1):77-82.

### Manuscript:

- (4) Roihuvuo-Leskinen H, Vainio M, Niskanen K, Lahdes-Vasama T. Pregnancies in women with vesicoureteral reflux in childhood.



## Abbreviations

AUA	American Urological Association
CAP	continuous antibiotic prophylaxis
CKD	chronic kidney disease
BBD	bladder and bowel dysfunction
BSA	body surface area
DMSA	dimercaptosuccinic acid scintigraphy
DV	dysfunctional voiding
EMG	electromyography
ESRD	end stage renal disease
EAU	European Association of Urology
GFR	glomerular filtration rate
HUCS	Helsinki University Central Hospital
IRSC	International Reflux Study in Children
IUGR	intrauterine growth retardation
LUT	lower urinary tract
MCG	mictiocyctography
MDRD	an estimated GFR calculated from serum creatinine using the Modification of Diet in Renal Disease Study equation
OAB	over active bladder
RN	reflux nephropathy
SFU	Society for Fetal Urology
SUI	stress urinary incontinence
UPP	urethral pressure profile
UTI	urinary tract infection
UVJ	ureterovesical junction
VCUG	voiding cystourethrogram
VUR	vesicoureteral reflux





# Abstract

Vesicoureteral reflux (VUR) is a common disease, affecting up to 18% of children. Its resolution rate is high, predictive factors for resolution being lower grade, and absence of renal scarring and lower urinary tract malfunction. Despite more effective diagnostic and treatment methods, some VUR patients still eventually became candidates for kidney transplantation.

This thesis aims at describing long-term outcomes (median follow-up time 36.7 years) in an unselected population of patients originally treated for primary VUR in childhood. Lower urinary tract (LUT) dysfunction occurrence in childhood VUR patients in the adulthood is assessed and its correlation with LUT related symptoms and urinary tract infection (UTI) is evaluated. Also ultrasound measured kidney volume relative to the kidney function is investigated in these earlier VUR patients. Finally, the pregnancy course in earlier VUR patients is explored, focusing on complications during pregnancies and possible predisposing factors behind the complications.

The population consist 137 (15 men) of 270 consecutive patients who have been diagnosed with primary VUR at Helsinki University Central Hospital (HUCS) between 1955 and 1965. 88 patients had been treated with prophylactic antibiotic therapy and 50 operatively during childhood. There were no definite indications for operative treatment, but usually it was the most severe cases that were operated on. 91 of the patients had dilating VUR in one or both kidneys.

All the patients underwent an urine flow test, an interview and a symptom questionnaire, blood tests, a urine sample and a renal ultrasound examination in adulthood. 27 women with either abnormal urine flow or normal flow but severe LUT symptoms were examined urodynamically. The pregnancy outcomes of 87 women were ascertained by interview and from the patient records of various hospitals in Finland. 43 age matched controls (6 men) went through the same protocol as the patients, except for the renal ultrasound and blood tests.

Assessment of LUT symptoms by means of the the questionnaire indicated that 53% of the patients had had at least one of the following symptoms: urgency, frequency, urgency incontinence or stress urinary incontinence. 40% had abnormal urine flow and 25% UTIs more than once a year in adulthood. Only 3% of the controls had abnormal flow ( $p<0.05$ ). The patients who had been operated on during childhood more often had abnormal flow (55%), mostly interrupted

(18%) or weak (27%) flow, than did those with conservative treatment (1% and 11%, respectively,  $p<0.05$  in both cases) and they had also more often had frequent UTIs during adulthood (31%) than the patients with conservative treatment (19%).

Despite the high frequency of storage symptoms, an overactive bladder was an infrequent finding (one patient) among the female patients with an abnormal flow curve or severe LUT symptoms examined urodynamically. Decreased sensitivity of the bladder was found in 41% of the patients, most often in patients with weak flow, in whom UTIs were also reported more often than in the other patients ( $p<0.05$ ). Dysfunctional voiding was found frequently, as abnormal sphincteric activity during voiding was found in 70% of the patients.

When ultrasound kidney size normalized to body surface was compared with kidney function a moderate correlation was found ( $r=0.42$ ). The kidneys affected with childhood VUR were smaller than those without any history of VUR. The occurrence of proteinuria or hypertension was not reflected in the patients with small kidney size, when renal scars were ruled out.

Renal function deterioration predisposed the women to complications during pregnancy. The women with renal scars detected by ultrasound during middle age more often had hypertension (33% vs. 13%,  $p<0.05$ ), proteinuria (40% vs. 21%,  $p=0.07$ ) and UTIs (42% vs. 23%,  $p=0.07$ ) during pregnancy than those without renal scars and the women with proteinuria during pregnancy had a higher rate of hypertension (44% vs. 15%,  $p<0.05$ ) and UTIs (55% vs. 23%,  $p<0.05$ ) than those without proteinuria. Though UTI was a common finding affecting one third of the pregnant women with childhood VUR, it was not associated with other complications. The fetal complication rate (30% of the women) was not affected by renal scarring, proteinuria or occurrence of UTIs during pregnancy or the severity of VUR during childhood.

To conclude with, adult patients with childhood VUR more often have lower urinary tract symptoms and findings than the general population. Women with renal scars and frequent UTIs are more prone to maternal complications during pregnancy and should be kept under special clinical observation. Assessing LUT symptoms and findings in the adult patients with childhood VUR may be helpful in estimating their risk of UTIs and UTI associated complications. Ultrasound can be used as a diagnostic tool estimating the risk of renal function deterioration in adult patients with childhood VUR.

# Tiivistelmä

Vesikoureteraalinen refluksi (VUR) eli virtsan takaisinvirtaus virtsarakosta munuasiin on tavallinen tauti, jonka esiintyvyydeksi lapsilla on arvioitu jopa 18 %. VUR:n korjaantumistaipumus on hyvä. Mitä lieväasteisempi tauti on, mitä vähemmän arpia on munuaiskudoksessa ja mitä vähemmän alempien virtsateiden toiminnassa on ongelmia, sitä paremmin VUR korjaantuu. Huolimatta tehostuneista diagnosointi- ja hoitomenetelmistä, pienellä osalla VUR-potilaista tauti edelleen johtaa munuaisten vajaatoimintaan ja munuaissiirtoon.

Tämän väitöskirjan tarkoituksena on selvittää lapsuudessa VUR:n sairastaneiden potilaiden pitkäaikaistuloksia seuranta-ajan mediaanin ollessa 36.7 vuotta. Aikuisten potilaiden alempien virtsateiden toiminnan häiriöiden esiintyvyyttä ja yhteyttä virtsatieinfektioihin (VTI) ja ultraäänellä mitattujen munuaistilavuuksien yhteyttä munuaisten toimintaan arvioidaan. Lisäksi tutkitaan raskauksien kulkua naisilla, jotka ovat sairastaneet VUR:n lapsuudessa, keskittyen raskausajan komplikaatioihin ja etsitään mahdollisia selittäviä taustatekijöitä komplikaatioille.

Tutkimusaineisto koostuu 270 peräkkäisestä potilaasta, jotka on diagnosoitu ja hoidettu Helsingissä Lastenkllinikalla vuosien 1955-1965 aikana primaarin VUR:n vuoksi. 137 potilasta, 122 naista ja 15 miestä kaikista tavoitetuista ja kutsutuista potilaista osallistui tutkimukseen. Näistä potilaista 88 on hoidettu antibiootein ja 50 leikkaamalla lapsuusiässä. Leikkaushoitoon ei ollut tarkkoja indikaatioita vaan tavallisesti vakavimmat tautitapaukset hoidettiin leikkaamalla. 91 potilaalla oli todettu munuaisaltaita laajentava VUR joko toisella puolella tai molemmiin puolin.

Aikuisiässä kaikille potilaille tehtiin virtsasuihkun virtausmittaus, heidät haastateltiin ja he täyttivät virtsaamisoireita kartoittavan kysymyskaavakkeen. Kaikilta otettiin verikokeita ja virtsanäyte sekä tutkittiin munuaiset ultraäänellä. 27 naista, joilla oli ollut joko poikkeava virtsasuihkun virtauskäyrä tai normaali käyrä, mutta hankalia alempien virtsateiden toiminnan ongelmia tutkittiin rakon painemittauksella sekä painevirtaustutkimuksella (urodynamiatutkimus). Raskauden kulku selvitettiin 87 naiselta haastatteluin ja sairauskertomuksista. 43 sairaalahenkilökuntaan kuuluvaa ikävakioitua kontrollia (joista 6 miehiä) tutkittiin samoin järjestyksessä kuin potilaat lukuun ottamatta munuaisten ultraääntä ja verikokeita.

Alempien virtsateiden oireita kartoittavan kyselyn perusteella 53 %:lla potilaista todettiin vähintään jokin seuraavista oireista: tiheävirtsaus, virtsapakko,

ponnistusinkontinenssi tai pakkoinkontinenssi. 40 %:lla todettiin epänormaali virtauskäyrä virtsasuihkun virtausmittauksessa ja 25 %:lla potilaista oli todettu VTI useammin kuin kerran vuodessa aikuisiällä. Vain 3 %:lla kontroleista todettiin epänormaali virtauskäyrä virtsasuihkun virtausmittauksessa ( $p<0.05$ ). Potilailla, jotka oli leikattu lapsuudessa VUR:n vuoksi, todettiin useammin epänormaali virtauskäyrä, joka oli tavallisimmin katkonainen (18 %), tai heikko (27 %) kuin niillä potilailla, jotka oli hoidettu konservatiivisesti (1 % ja 11 %, vastaavasti,  $p<0.05$  molemmissa). Operatiivisesti hoidetuilla potilailla oli myös useammin toistuvia virtsatieinfektioita aikuisiällä.

Vaikka naispotilailla oli paljon virtsarakon täyttöön ja virtsan varastointiin liittyviä oireita, rakon yliaktiivisuus painemittauksessa oli harvinainen löydös (yksi potilas) niillä 27 naisella, jotka tutkittiin urodynamiatutkimuksella.

Alentunut tunto virtsarakon täyttöön liittyen todettiin 41 %:lla naispotilaista, usein potilailla oli ollut heikko virtaus virtsasuihkun virtausmittauksessa. Näillä naisilla, joilla oli alentunut rakon tunto, todettiin muita potilaita useammin VTI:ita ( $p<0.05$ ). Dysfunktionaalinen virtsaaminen (rakkolihaksen ja sulkijalihaksen dyssynergia) oli tavallinen löydös, sillä 70 %:lla potilaista todettiin paine-virtaustutkimuksessa epänormaalia sulkijalihaksen aktiivisuutta.

Ultraäänellä mitattu munuaisten tilavuus suhteutettiin kehon pinta-alaan, jotta munuaisten koko saatiin vertauskelpoiseksi muiden potilaiden kanssa. Näin mitatun tilavuuden ja munaisten toimintakokeen välillä todettiin kohtalainen korrelaatio (Pearsonin  $r=0.42$ ). Munuaiset, joihin oli ollut takaisinvirtausta, olivat pienempiä kuin munuaiset, joihin takaisinvirtausta ei ollut. Valkuaisvirtsaisuuden ja korkean verenpaineen esiintyvyys ei lisääntynyt niillä potilailla, joilla oli pienet (mutta arvettomat) munuaiset.

Naiset joilla munuaisten toiminta oli heikentynyt, olivat alttiimpia raskaudenaikaisille komplikaatioille. Raskaudenaikaista korkeaa verenpainetta (33 % vs. 13 %,  $p<0.05$ ), virtsan valkuaista (40 % vs. 21 %,  $p=0.07$ ) ja virtsatieinfektioita (42 % vs. 23 %,  $p=0.07$ ) todettiin useammin niillä naisilla, joilla keski-iässä todettiin ultraäänellä arpia munuaisissa kuin naisilla, joilla munuaisarpia ei todettu. Samoin naisilla, joilla todettiin virtsassa valkuaista raskauden aikana, oli merkitsevästi enemmän korkeaa verenpainetta (44 % vs. 15 %,  $p<0.05$ ) ja virtsatieinfektioita (55 % vs. 23 %,  $p<0.05$ ) raskauden aikana kuin niillä naisilla, joilla ei todettu raskauden aikaista virtsan valkuaista. Vaikka VTI:ta todettiin jopa kolmasosalla naisista raskausaikana, siihen ei liittynyt muita komplikaatioita. Sikiöihin kohdistuvien raskausajan komplikaatioiden määrään eivät vaikuttaneet äitien munuaisarpien esiintyvyys, raskauden aikaisen proteinurian tai VTI:n esiintyvyys eikä VUR:n vaikeusaste.

Lapsuudessa VUR:n sairastaneilla potilailla on aikuisina muuta väestöä enemmän alempien virtsateiden toimintahäiriöiden oireita ja löydöksiä, ja niiden tutkiminen on hyödyllistä VTI:hin ja siihen liittyvien komplikaatioiden riskin ar-

vioinnissa. Lapsuudessa VUR:n sairastaneilla naisilla, joilla on munuaisarpia tai toistuvia VTI:ta on tutkimuksemme mukaan suurempi riski raskausajan komplikaatioihin, minkä vuoksi he vaativat tarkkaa kliinistä seurantaa. Ultraääntä voidaan käyttää kliinisessä työssä kun arvioidaan riskiä munuaisten toiminnan huononemiseen aikuisilla potilailla, jotka ovat sairastaneet VUR:n lapsuusiässä.



# 1 Review of the literature

## 1.1 Embryology and anatomy

### 1.1.1 *Normal development of the urogenital system*

#### 1.1.1.1 *Renal and ureteral development*

The primitive 3-week embryo consists of three layers: the ectoderm, mesoderm and endoderm. The kidney and ureter start to differentiate from the mesodermic tissue in the 4<sup>th</sup> week. There are three kidney systems during fetal life: the pronephros, mesonephros and metanephros. The pronephros disappears at the end of the 4<sup>th</sup> week. The mesonephros forms the urogenital ridge and the mesonephric or Wolffian duct. The metanephros then appears in the 5<sup>th</sup> week and forms the permanent kidney excretory system (Sadler 1990).

The Wolffian duct grows out a diverticulum to the metanephric blastema, the ureteric bud. The metanephric blastema moulds over the distal end of the ureteric bud, which dilates and forms the primitive renal pelvis. The ureteric buds split, forming two new buds, which then continue to subdivide several times and elongate. Finally, the ureteric buds form the collecting tubules, the minor and major calyces and the ureter. The initiation of the tubules and their branching into the collecting system is stimulated by the metanephric tissue (Tanagho 1981, Batourina, Tsai et al. 2005, Sainio, Suvanto et al. 1997).

The metanephric mesoderm gives rise to the excretory units of the kidney. At the end of each collecting tubule there is a metanephric tissue cap. The tubule induces the cells of the metanephric blastema to form renal vesicles, which, together with capillaries called glomeruli, give rise to the excretory units, the nephrons. The proximal end of each nephron forms the Bowman's capsule and the distal end constitutes an open connection with the collecting system (Sadler 1990).

#### 1.1.1.2 *Bladder and urethra development* (Fig. 1)

Part of the endoderm-lined yolk sac incorporates into the body cavity during the cephalocaudal and lateral folding of the embryo and forms the primitive gut by the end of the first month. The primitive gut as such can be divided into 4 sec-



tions: the pharyngeal gut, the foregut, the midgut and the hindgut. The endodermic tissue forms the epithelium of the primitive gut and the mesoderm forms the muscular and the peritoneal parts (Sadler 1990).

The allantois together with the terminal part of the hindgut forms the cloaca. The cloaca is in contact with the ectoderm, forming the cloacal membrane in the contact area. The urorectal septum, which is formed in the angle between the allantois and the hindgut divides the cloaca into anterior and posterior parts, known as the primitive urogenital sinus and the anorectal canal, respectively. At 7 weeks the urorectal septum and the cloacal membrane unite, forming the perineum. The cloacal membrane then divides to form the urogenital membrane anteriorly and the anal membrane posteriorly (Sadler 1990, Tanagho, Nguyen 2008).

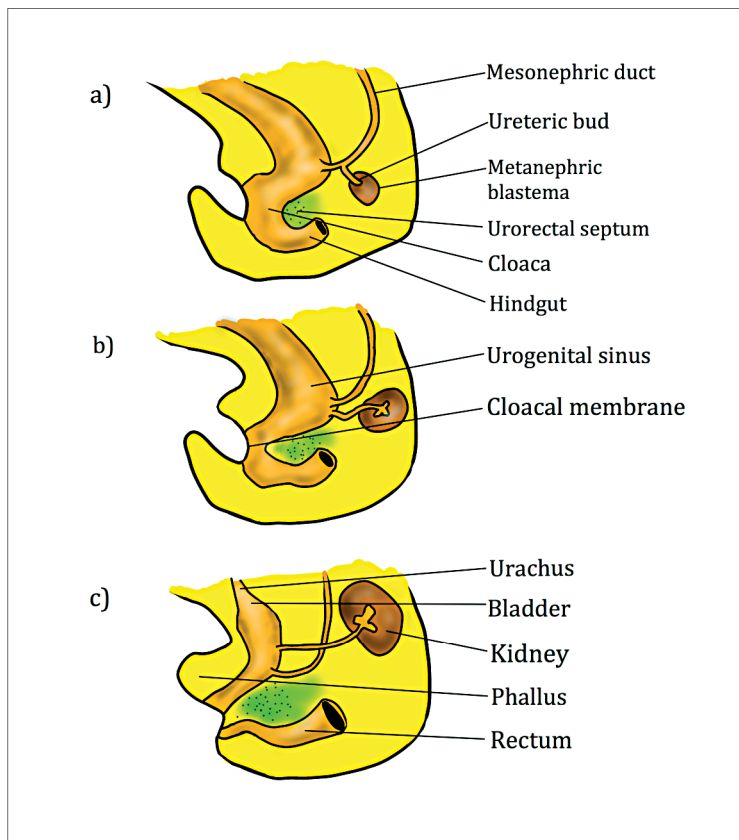


Figure 1.  
Embryology of the urogenital system at a) end of the 5<sup>th</sup> week, b) 7 weeks  
c) 8 weeks of age.

The primitive urogenital sinus can be divided into the urinary bladder, the pelvic part of the urogenital sinus and the phallic part. When the lumen of the allantois is obliterated, it becomes the urachus (the future median umbilical ligament), which connects the bladder to the umbilicus (Sadler 1990). The pelvic part of the urogenital sinus gives rise to the prostatic and membranous parts of the urethra in males and the whole urethra in females. The phallic part of the urogenital sinus forms the lower part of the vagina and vaginal vestibule in females and the distal part of the urethra in males (Tanagho, Nguyen 2008).

The caudal parts of the mesonephric ducts become part of the bladder during the time when the cloaca is dividing. The ureteric bud, which has originated earlier from the mesonephric duct, enters the bladder separately from the duct. The ureteral orifice first opens at the neck of the bladder, but as the bladder grows and the kidneys move further in a cranial direction, the entrance of the ureter shifts nearer to the normal position (Peters, Schlusser et al. 2012). Finally, the ureter enters the bladder in an oblique position through the muscle layer of the bladder wall. The mesonephric ducts move close together and enter the prostatic urethra to become the ejaculatory ducts. The area between the entrance to the ureters and the mesonephric ducts is thus of mesonephric origin and is called the trigonum of the bladder. The other part of the bladder is formed from the urogenital sinus, which is of endodermal origin. Later it is the urothelium, which is also of the endodermal origin, that lines the inside of the whole bladder (Sadler 1990). More recent publications have questioned this theory of the trigonum being mesonephric origin, and it has now been hypothesized in the new theory of ureteric maturation that mesodermal cells originating the mesonephric duct are removed by apoptosis and that the origin of the trigonum is endodermal (Batourina, Tsai et al. 2005, Tanaka, Ishii et al. 2010).

The kidney first lies in a sacral position and obtains its blood supply from the pelvic branches of the aorta. As the embryo develops, the kidney ascends to a lumbar position and rotates, this occurring during the fourth to ninth weeks of gestation (Decter 1997). The lower arterial branches degenerate and the kidney is vascularized by arteries originating from the aorta at a higher level (Park 2012). The kidneys become functional during the second half of the pregnancy, but they do not excrete waste products during fetal life (Sadler 1990).

Normal nephrourogenesis requires complex transactions between genes and transmitters. There are over 30 genes involved in the development of mammalian kidneys (Park 2012), constituting a complex regulatory network that has been well demonstrated in animal models (Itäranta, Lin et al. 2002, Sainio, Suvanto et al. 1997, Batourina, Tsai et al. 2005). In human studies certain genomic disruptions have been identified in genetically inherited syndromic diseases involving urinary tract anomalies. These studies have shown that VUR and the related renal

dysplasia may be caused by a complex gene regulation network, although the gene(s) responsible for regulation in the case of primary VUR have not yet been found (Murer, Benetti et al. 2007, Feather, Malcolm et al. 2000).

### *1.1.2 Abnormal development of the urogenital system*

The place where the ureteric bud makes contact with the metanephric blastema determines where the ureteral orifice is placed. If the ureteric bud originates too far in a caudal direction in the Wolffian duct, the ureteric orifice will be located cranially in the bladder and the tunnel inside the muscle layer will be too short, causing vesicoureteral reflux (VUR) (Sadler 1990). In a double system, two ureteric buds develop, with that forming the upper pole developing later and more cephalad. The upper pole ureter will have a low abnormal entrance in the bladder or else an ectopic entrance in the vagina, urethra or epididymal region. The ureteric bud forming the lower pole is usually in the normal position and forms a normal ureter (Peters, Schlusser et al. 2012).

As the metanephric blastema is poorly differentiated at the point of ectopic budding, the Wolffian duct cannot induce the formation of the normal excretory system, and kidney dysplasia occurs. Renal agenesis is probably caused by early degeneration of the ureteric bud. A double system may also occur if the ureteric bud splits too early and the metanephric blastema also splits in-to two parts, whereupon each ureter will have its own pelvis (Sadler 1990, Murer, Benetti et al. 2007). The new theory of ureteric maturation regards ureterovesical junction abnormalities as resulting from disturbances in the apoptosis of mesonephric cells (Peters, Schlusser et al. 2012).

According to the “non-union” theory, nonunion of the collecting and excretory tubules leads to congenital dysplastic kidney disease, although others see the reason for these cysts as lying in abnormal formation of the collecting system (Sadler 1990). Some of the original arteries from the lower part of the aorta, referred to as supernumerary arteries, may persist during the kidney ascent, or if the rotation or ascent of the kidney is disturbed the kidney may persist in an ectopic position as a pelvic kidney. Horseshoe kidney is also a consequence of abnormal ascent, in which the kidneys are pushed close to each other during the ascent that their lower poles fuse (Sadler 1990, Decter 1997).

### *1.1.3 Anatomy of the urinary tract*

The kidney is a paired organ located on the retroperitoneum in both sides of the vertebral column. The right kidney is situated a little lower than the left one be-

cause of the liver. The kidney can be divided into the outer layer, the cortex, and the inner layer, the medulla and pelvis. The nephrons, the functional units of the kidney are situated in the cortex, while the collecting tubules lie in the medulla or in the pyramid. The kidney vessels are situated in front of the renal pelvis, from which the ureter leaves the kidney. The kidney receives its blood supply from the renal arteries, which originate from the aorta (Anderson, Cadeddu 2012).

The functional units in the kidney are the nephrons, of which there are approximately one million in the young adult kidney. The glomerulus, a capillary tuft, is surrounded by a proximal tubule forming the Bowman's capsule. Blood is filtered through the glomerular capillaries and the filtrate is collected by the Bowman's capsule. The filtrate first flows through the proximal convoluted tubules, the ascending and descending parts of tubules, called the Henle's loop, and the distal convoluted tubules, to the collecting tubules and collecting ducts, where it finally empties into the renal papilla (Sadler 1990, Chung, Sommer et al. 2012).

The ureter, which transports the urine to the urinary bladder leaves the kidney at a point posterior to the artery and vein. The upper ureter gains its blood supply from the nephric arteries, while the internal spermatic or ovarian arteries feed the middle third of the ureter and the pelvic ureter receives its arterial supply from the common and internal iliac arteries, the inferior vesical artery and the uterine artery (Tanagho 1981, Tanagho, Nguyen 2008). In one third of all human individuals the ureteral vessels run in a plexiform mesh along the intramural layer of the ureter, forming very few anastomoses. The pelvic ureter obtains both its adrenergic and cholinergic innervation from the pelvic plexus (Tanagho, Nguyen 2008).

The ureters have an intramural, oblique course upon entering the bladder. The distal part of the ureter lies in between the mucous and muscle layers of the bladder, forming a submucous course, or "tunnel". The intramural and submucous course of the ureters forms a passive valve mechanism at the ureterovesical junction that prevents urine backflow to the ureters when the bladder is filling and the intravesical pressure increase squeezes the submucous tunnel (Stephens, Lenaghan 1962). Hutch demonstrated in 1961 (Hutch 1961) how a decrease in the intravesical length of the ureters increases the frequency of VUR. Muscular attachments of the ureters to the trigonum, a smooth triangular area at the base of the bladder, as well as the oblique course of the ureters, are important factors in forming a functional valve mechanism (Johnston 1962, Tanagho, Hutch et al. 1965, Zatz 1965). The detrusor muscle forms a meshwork of muscle fibre overlaid by a connective tissue layer, the lamina propria, while the epithelium of the bladder is formed from a transitional epithelium called the urothelium. The muscular layer in the bladder neck consists of three distinct layers: the inner longitudinal, middle circular and outer longitudinal layers. In males the middle layer

forms the preprostatic, internal sphincter and the outer longitudinal layer a loop running from the back of the bladder to its anterior side. There is both parasympathetic and adrenergic innervation of the preprostatic sphincter. In females the adrenergic innervation and the anatomic orientation of the muscular fibres are much vaguer (Chung, Sommer et al. 2012, Jung, Ahn et al. 2012).

The anatomy of the ureterovesical junction (UVJ) has been described by Tanagho (1963). The spirally oriented muscle fibres become longitudinal at the distal end of the ureter. The ureter passes through the muscular wall of the bladder obliquely and then proceeds between the muscular layer and the urothelium before entering the bladder via the ureteral orifice. The layer of smooth muscle in both ureters continues in a fan-like shape in the bladder base, forming a trigonum between the two ureteral orifices and the orifice of the urethra (Chung, Sommer et al. 2012).

The bladder is innervated by the parasympathetic cholinergic nerves of the pelvic plexus, which originate from the spinal cord in the anterior roots S2-S4. Parasympathetic activation contracts the detrusor muscle during micturition (Birder, De Groat et al. 2010), and it has been suggested that the exiguous sympathetic innervation of the bladder may mediate detrusor relaxation. In males the bladder neck has a rich sympathetic innervation, but this is not the case in females. Sympathetic activation results in closure of the bladder neck during bladder filling. There are also neurons in the bladder and bladder neck which contain nitric oxide synthase and are assumed to participate in relaxation of these areas. Both the sympathetic and parasympathetic fibres carry afferent innervation from the bladder to the thoracolumbar and sacral ganglia (Anderson, Cadeddu 2012). The pelvic plexus, which contains both the sympathetic and parasympathetic neurons, is involved in reproduction and micturition. The main portion of the pelvic plexus is situated adjacent to the bladder wall near the ureterovesical junction (Leissner, Allhoff et al. 2001). The intrinsic sphincter of the bladder is innervated by activity of the sympathetic nervous system originating from T10-L2. The extrinsic, voluntarily regulated sphincter is controlled by the pudendal nerve, originating from the sacral roots (Birder, De Groat et al. 2010, Jung, Ahn et al. 2012).

#### *1.1.4 Kidney function*

The most important function of the kidneys is glomerular filtration. Under normal conditions the blood flow to the kidneys, amounting to 20-30% of the cardiac output, takes place via the renal arteries, which divide into progressively smaller ones, and finally into the afferent arterioles and the capillaries known as glomerular arteries. In the glomerular arteries the plasma is filtered through the glomerular membrane. The glomerular filtration rate (GFR) is determined by

both the hydraulic and oncotic pressure difference between the glomerular capillary and the Bowman's space and by the permeability of the glomerular membrane, according to Starlings law (Starling 1896). The GFR equilibrium is well regulated and maintains a constant GFR (Shoskes, McMahon 2012).

### *1.1.5 Urinary tract function*

The ureter carries urine from the kidney pelvis to the urinary bladder. As the pressure in the pelvis increases with volume, urine is pushed to the proximal ureter, where a pacemaker initiate a peristaltic wave that is transmitted through the muscular layer of the ureter. These peristaltic waves carry the urine in boluses to the distal ureter and through the ureterovesical junction to the bladder (Weiss 2012).

The lower urinary tract has two purposes: to store urine and to eliminate it. Storage and micturition are controlled by a complex neural system situated in the brain, the spinal cord and the peripheral ganglia (Fowler, Griffiths et al. 2008). In order to store urine the bladder needs to accommodate to the increasing volume without any increase in intravesical pressure. This "compliance" is generated by the elastic and viscoelastic properties of the bladder. The cholinergic sympathetic nerve system has also been shown to inhibit any rise in pressure during bladder filling (Wein 2012). The bladder outlet must be kept closed during the storage, even when the intra-abdominal pressure increases, e.g. when coughing. During filling, the guarding reflex activated by the efferent pudendal nerve increases the urethral pressure via activation of the striated sphincter, while the parasympathetic nerves which innervate the detrusor are inhibited (Fowler, Griffiths et al. 2008).

As distention of the bladder increases, the micturition reflex is turned on in the brain's pontine micturition centre. The urethra is relaxed by the inhibition of the sympathetic outflow and the detrusor contracts in response to the sacral parasympathetic outflow. Because micturition is a voluntary action, the pontine micturition centre is nevertheless controlled by the higher centres of the CNS, and thus micturition occurs only at times and places that are socially acceptable (Fowler, Griffiths et al. 2008). During the micturition the smooth muscle of the bladder has to contract in a coordinated manner and so that both the smooth and striated sphincters open simultaneously (Wein 2012).

### *1.1.6 Voiding dysfunction*

The International Continence Society and the International Urogynaecological Association define female voiding dysfunction as "abnormally slow and/or incomplete micturition based on symptoms and urodynamic investigations" (Haylen,

De Ridder et al. 2010). In their recent review, Robinson et al. (2012) propose 100ml as the normal limit for residual urine in females in urodynamic examinations, although no clear-cut consensus regarding this limit can be found in the literature.

In the EPIC study reported on by Irwin et al. in 2006 (Irwin, Milsom et al. 2006), 59 000 randomly selected men and women over 18 years were contacted in five countries (Canada, Germany, Italy, Sweden, UK) and over 19 000 of these were interviewed by telephone. The outcome was that 62% of the women over 40 years and 67% of the men had LUTS in this population based survey, 59% of the women and 51% of the men reported to have storage symptoms, 20% of the women and 26% of the men had voiding symptoms, and symptoms related to OAB were reported by 13% of the women and 11% of the men.

## 1.2 Classification of VUR

The severity of VUR is assessed from grade I to grade V according to the International Classification of VUR Grading (Figure 2.), depending on how far back the urine flows, as described by Heikel and Parkkulainen in 1966 (Heikel, Parkkulainen 1966). This grading was originally based on voiding cystourethrography (VCUG). In grade I reflux the contrast medium can be seen in the ureter but it does not reach the renal pelvis, in grade II it can be seen in the ureter and the pelvis, but no dilatation is present and the fornices are normal, while in grade III the ureter and the collecting system in the kidney are mildly or moderately dilated, but the fornices may be normal or mildly deformed. In grade IV the ureter is moderately dilated and may or may not kink, the collecting system is moderately dilated, the fornices are blunt but the impressions of papillae are still visible over most of the calices and finally in grade V there is gross dilatation and kinking of the ureter, the collecting system is severely dilated and the papillary impressions are no longer visible in the majority of the calices. Grades I and II are referred to as nondilating reflux and grades III to V as dilating reflux. Primary VUR does not involve any anatomical or neurological disturbances causing urethral obstruction or a pressure gradient in the kidneys. When such contributing aetiologies are present the condition is called secondary VUR (Lebowitz, Olbing et al. 1985, Heikel, Parkkulainen 1966).

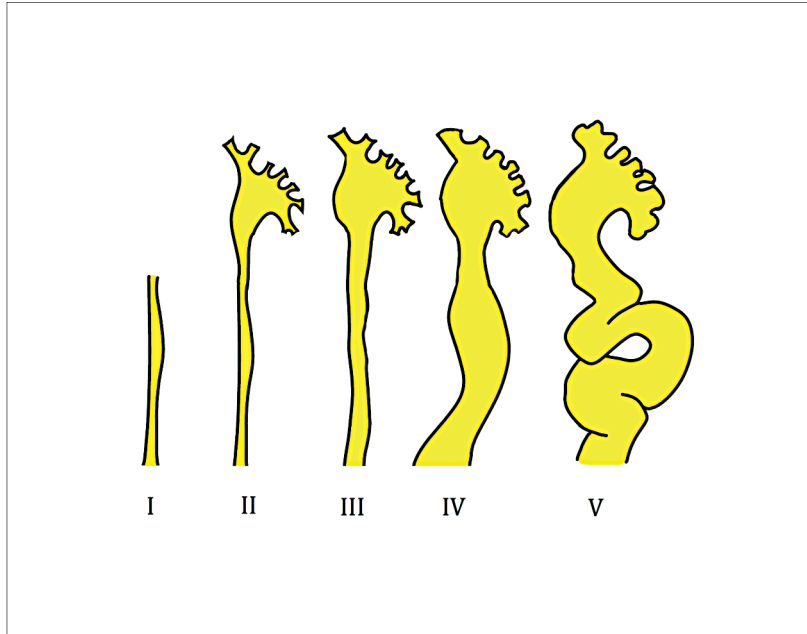


Figure 2.  
The International VUR grading. Modified from Heikel and Parkkulainen  
(Heikel, Parkkulainen 1966).

### 1.3 Incidence of VUR

The prevalence of primary VUR in a healthy population has earlier been estimated at 0.4-1.8% (Bailey 1979), based on reports published from the 1950's to the 1970's. At that time VUR was almost always detected after symptomatic urinary tract infection (UTI) and the prevalence is thus based on this patient population. The prevalence of UTI in children is estimated to be 5-10% (Hellström, Hanson et al. 1991, Shaikh, Morone et al. 2008), and VUR is diagnosed in 30-40% of UTI patients (Jacobson, Hansson et al. 1999). In a more recent review by Sargent (Sargent 2000), from a time when patients with antenatal hydronephrosis (seen in fetal ultrasound) and siblings of VUR patients were also screened for VUR, its prevalence in asymptomatic children was found to be 9% in the published literature and 31% in patients with UTI. According to up-to-date meta-analysis



of Skoog et al. (2010), 16% of patients with prenatally diagnosed hydronephrosis have VUR, as do 32% of the first-degree relatives of VUR patients.

Since the diagnosis of VUR is based on VCUG, which is an invasive examination and exposes the subject to ionizing radiation, it is not justified to screen general populations for this condition, and there are very few papers published in which VCUG data have been collected in a normal healthy population. Köllerman et al. examined in 1967 with VCUG 102 children aged 0-5 years admitted to hospital for various reasons and found VUR in 60% out of below one-year old children and in none of children over 5 years of age (Köllermann, Ludwig 1967). Unfortunately, others have not been able to repeat this research. Estimates and published data regarding the prevalence of VUR differ depending on patients' age, gender and ethnic origin, with figures varying in the range 1-18% depending on the mean age and degree of selection of the patient series (Sargent 2000). It must be admitted, however, that the exact prevalence of VUR in the general population is unknown.

## 1.4 Aetiology of VUR

The anatomical structure of the ureterovesical junction as described in section 1.1.3, is that of a passive valve that lets urine flow from the ureter into the bladder but not from the bladder into the ureter. If the structure of the UVJ is anatomically abnormal its function will also be disturbed. A ratio of 5:1 between the intramural ureteral length and the diameter of the ureter, as stated by Paquin in 1959 (Paquin 1959), has formed the basis for the surgical treatment of VUR. The intramural tunnel has proved to increase in length as the fetus matures, and it is known that the ratio of its length to the ureteral diameter at the vesicoureteral junction is much lower than 5:1 in newborns. Also, it has been observed recently that the smooth muscle and the innervation of the ureter play important roles in ureterovesical valve function (Radmayr, Schwentner et al. 2009).

The pressure conditions around the UVJ similarly play an important role in its function. In order to ensure the normal flow of urine from the ureter to the bladder, the ureteral pressure needs to rise above the pressure inside the bladder. If pressure in the bladder exceeds the intraluminal pressure of the ureter this flow will be hindered. This is well demonstrated in patients with neurogenic high pressure bladder (Sillen 2008), and impaired ureteral function also brings on the same effect. It has been postulated that decreased peristaltic activity in the ureters may form part of the aetiological mechanism of VUR (Weiss, Biancani 1983).

### *1.4.1 The genetic aetiology of VUR*

The genetic basis is a significant factor in the pathogenesis of primary VUR. First-degree relatives of VUR patients have been reported to have a 30 to 50-fold higher increase in incidence of VUR than is observed in the general population (Noe, Wyatt et al. 1992), and the prevalence in identical twins is 100% (Kaefer, Curran et al. 2000).

The prevalence of VUR in children differs between ethnic groups. Melhem et al. (2007) showed on their work of children with urinary tract infection that black children had VUR associated with urinary tract infection significantly less frequently than did white children up to 10 years of age, at which point the prevalence in white children gradually decreased to the level of the black children.

Feather et al. (2000), in their study of 7 European VUR families, found dominant inheritance of primary VUR with a susceptible locus on chromosome 1, and noted that the inheritance of VUR was potentially polygenic and was dominant only in some of the families. Kelly et al. (2009) investigated DNA samples from 219 sibling pairs with VUR and found a moderately significant signal on the chromosome 10 q arm, while Conte et al. (2008), in their DNA study of Italian VUR families found a dominant inheritance pattern in some of them, with genome loci on chromosomes 1, 3, 4 and 22. Like the other authors mentioned above, they concluded that primary VUR is a genetic condition, albeit a heterogeneous one.

### *1.4.2 The urodynamic basis for VUR*

A well-known association between VUR and lower urinary tract dysfunction exists in patients with neurogenic bladder or a posterior urethral valve (Hinman, Baumann 1973), and there are numerous papers demonstrating a relationship between primary VUR and bladder function (Koff 1992, Koff, Wagner et al. 1998, Ural, Ulman et al. 2008). The evidence as to whether treatment of such a bladder dysfunction will improve the resolution of VUR remains controversial, however (Sillen 2008).

Lower urinary tract (LUT) dysfunction in children can be divided into overactive bladder (OAB) and dysfunctional voiding (DV), with definitions that conform to the standards recommended by the International Children's Continence Society (Nevés, von Gontard et al. 2006). OAB refers to bladder filling phase syndrome, where the detrusor muscle contracts in an uncontrolled manner and the patient has to constrict the sphincter voluntarily in order to remain continent. This unstable, over-active dysfunction manifests itself in urgency, incontinence, squatting and other holding manoeuvres (Sillen 1999).

DV describes a voiding phase dysfunction, which takes on a more severe form in association with UTIs and renal damage (Sillen 2008). Here the detrusor muscle contracts in the normal way but the sphincter mechanism does not open properly and this raises the intravesical pressure abnormally high during micturition. This is said to be a learned mechanism resulting from the uncontrolled detrusor contractions that manifests itself when the child is learning to stay dry, becoming evident in the form of day-time and night-time wetting, interrupted voiding and recurrent urinary tract infections. The most serious manifestation is “non-neurogenic neurogenic” bladder, as described Hinman in 1973 (Hinman, Baumann 1973). Constipation and fecal retention is often seen in these children (Koff, Wagner et al. 1998). Underactive detrusor, formerly called lazy bladder is a condition resulting from long-term dysfunctional voiding (Nørgaard, Van Gool et al. 1998).

The incidence of OAB in a population with VUR is reported to be up to 55% and DV from 25 to 68%, depending on the ages of the patients’ (Sillen 1999, Koff, Murtagh 1983, Seruca 1989). Fractionated micturition, frequent small voids and small bladder capacity have been reported in half of the infants with VUR (Jansson, Hanson et al. 2000, Sillen 1999), while other authors have found older children with VUR increased bladder capacity to be notably more frequent than among non-VUR patients (Tamminen-Möbius, Olbing et al. 1994, Zerlin, Chen et al. 1993).

Bladder dysfunction can be investigated by urine flowmetry and residual measurement, a non-invasive and easily available method. Voided urine volumes are measured over time, the strength and continuity of the flow are evaluated and the amount of residual urine is assessed with ultrasound (Abrams, Cardozo et al. 2003). A more accurate, but also more invasive method is urodynamic examination, which measures not only the voiding phase but also the storage phase. Here the bladder is slowly filled by means of a special catheter which also measures pressure inside the bladder, while that outside the bladder is recorded with a rectal probe. The difference between the bladder pressure and rectal pressure is calculated, and this is taken to define the detrusor pressure. The examination is performed with the patient awake, and its invasiveness means that the patient is required to cooperate well, which can be difficult with children. The limiting values must also be adjusted according to the patient’s size when investigating children (Nitti 2012).

Voiding dysfunction has also been found as a part of the normal development of healthy infants. Bachelard and Sillen with their research group performed urodynamic and VCUG examinations on infant siblings of VUR patients and found VUR in 16% of them (Bachelard, Sillen et al. 1999). They also found unexpectedly high voiding pressures (127cmH<sub>2</sub>O) in healthy male infants without VUR and low bladder capacity (20ml) in all the healthy infants, but they did not find

bladder instability in the healthy infants as they did in the infants with UTI or dilating reflux (Bachelard, Sillen et al. 1998, Sillén, Hellstrom et al. 1999). The voiding pattern of intermittent pelvic floor activity and fluctuating voiding pressure observed in these healthy infants indicated physiological bladder-sphincter dyscoordination and immature voiding function (Bachelard, Sillen et al. 1999).

Ural et al. (2008) found VUR in 46% of a series of 348 children with overactive bladder or dysfunctional voiding who had been admitted to a tertiary hospital. All the patients underwent a urodynamic examination and those with urinary tract infection were also subjected to VCUG. The patients with VUR were significantly younger than those without VUR, and continent children presented with VUR significantly more often than did incontinent children. The reflux resolved in 40% of cases during a one-year follow-up accompanied by medical and instructional therapy. A higher cystometric bladder capacity and lower grade of VUR predicted a better VUR resolution rate.

## 1.5 Pathogenesis of VUR

### 1.5.1 Urinary tract infections in VUR patients

UTI is a common disease among children, affecting 5-10% (Hellström, Hanson et al. 1991), and the incidence of VUR in patients with UTI is 30-50% (Tekgül, Riedmiller et al. 2012). Hutch described a causal relationship between VUR and pyelonephritis in paraplegic patients for the first time in 1952 (Hutch 1952), and Ransley and Risdon later demonstrated this in animal experiments (Ransley, Risdon 1981). In most children the diagnosis of VUR is still made during the investigation of urinary tract infection, and a VUR prevalence of 35% was reported in a recent Finnish study of children younger than 5 years referred to hospital on account of suspected or confirmed UTI (Venhola, Hannula et al. 2010).

The usual pathogens causing UTI in VUR patients are *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*, with *E. coli* responsible for 89% of the infections. The grade of VUR has been reported to be higher in patients with some other organism than in those with *E. coli* infection (Carpenter, Hoberman et al. 2013).

Most bacteria causing UTI originate from the bowel flora. The bacterial virulence factors play a role in which bacteria invade and the extent of infection. Uropathogenic *E. coli* strains express adhesive characteristics (pili, fimbriae and adhesins) that help them to attach to urinary tract tissue and avoid clearance with the flow of urine (Schaeffer, Schaeffer 2012, Mulvey 2002). The pyelonephritis associated P-fimbriae were found frequently (73%) in children with pyelonephri-

tis but less often in children with cystitis (23%) in a Finnish study of Elo et al. (Elo, Tallgren et al. 1985).

The Swedish Reflux Study followed small children (aged between 1 and 2 years) with dilating VUR for the next two years, dividing them into three groups: those with surveillance only, those receiving continuous antibiotic therapy (CAP) and those receiving endoscopic bulking injection therapy. The authors found that the surveillance only group had 20% more recurrent febrile UTIs than other groups, but only among the girls. They also found that new renal scar formation formed more frequently in the patients with recurrent febrile UTIs than in those without infections. They concluded that small girls with dilating reflux benefit from CAP, this protects them from recurrent febrile UTIs (Brandström, Esbjörner et al. 2010).

### *1.5.2 Renal scars in VUR patients*

Renal scarring associated with VUR can be divided into two categories: congenitally dysplastic, small kidneys, as seen in patients with severe grade of VUR (Lama, Russo et al. 2000), and an acquired form in which intrarenal reflux causes the kidneys to scar in a segmental manner (Risdon 1993). Intrarenal reflux is urine backflow from the renal pelvis to the collecting system, and the urine in question can be either sterile, as described by Bailey in 1981 (Bailey 1981), in which case only the hydrostatic conditions cause any parenchymal damage, or contaminated, whereupon renal scarring is mediated by the bacterial products and inflammation (Risdon 1993). Wennerström et al. (2000) investigating a cohort of children with UTI, found renal scarring at the time of diagnosis in 86% of the boys and 30% of the girls, the difference being probably due to etiology: congenital damage in the boys and acquired scarring, related to pyelonephritis in the girls (Blumenthal 2006).

Most of the renal scars associated with VUR already exist at the time of diagnosis, and there are also many published papers that indicate that new renal scars tend to appear at an early age. In the International Reflux Study in Children (IRSC, for a more detailed description of its protocol, see Section 1.8) 49% of the patients with VUR had renal scars upon enrolment and most of the new renal scars appeared during the first 5 years, so that only 2 new scars were detected after 5 years follow-up. The younger the patients were, the more frequently new scars were detected. New renal scars also appeared in the boys, 86% whom were aged less than two years. After 10 years follow-up 13% of the patients had acquired new scars. Scars were detected equally in the surgical and medical treatment groups (Jodal, Smellie et al. 2006, Olbing, Smellie et al. 2003). In the Swedish Reflux Study, 61% of the small children with dilating VUR followed

up for two years had renal scars at enrollment (54% of the girls and 73% of the boys) (Brandström, Esbjörner et al. 2010), while new scars were seen during the follow up in 7% (10% of the girls and 3% of the boys) of the patients. New renal scars were seen more frequently in the patients with recurrent febrile UTIs than in those without (Brandström, Nevéus et al. 2010). Smellie et al. did not find any new renal scars in 193 childhood VUR patients examined during adulthood as compared with imaging results obtained during childhood (mean follow-up time 20 years) (Smellie, Prescod et al. 1998).

The true rate of occurrence of new renal scars in VUR patients is not known nor is it known whether there is a “safe” age, when new renal scars stop appearing, as only a limited number of trials comparing either surgical or medical treatment with observation alone are available. The results of the Randomized Intervention for Vesicoureteral Reflux (RIVUR) study are expected to shed some light on this insufficiently studied aspect. RIVUR is a randomized, double blind, placebo controlled trial currently taking place in the USA which is designed to provide information on prophylactic antimicrobial therapy for children with VUR and its effects on renal scarring and recurrent infections by comparing medical treatment with a placebo. Enrolment was completed in 2011, and according to preliminary reports, 607 patients (median age 12 months) were enrolled after their first (91%) or second UTI and had VUR of grades I to IV as assessed by VCUG, with grades II and III accounting for 80% of the patients. Renal scars were detected in 4% of the patients (Carpenter, Hoberman et al. 2013).

Renal scars may also be associated with pyelonephritis without VUR. In a Swedish cohort of children under 6 years of age experiencing their first symptomatic UTI, one third of those with pyelonephritis ended up with renal scarring detected in DMSA one year after the index infection (Stokland, Hellstrom et al. 1996). Correspondingly, Taskinen and Rönholm (Taskinen, Rönholm 2005), assessing 64 hospitalized Finnish children with a median age of 2.9 years having pyelonephritis for the first time found that 11 of them had grade II-V VUR. Eventually 21% of the patients developed renal scarring visible in DMSA during the two years of the follow-up. Three out of the 12 patients who had renal scarring at the two-year follow-up had VUR.

Renal scarring may detract from renal growth and function. Bilateral scarring may lead to renal insufficiency (Tekgül, Riedmiller et al. 2012), and 10-20% of patients with renal scarring related to VUR are reported to develop renal hypertension or end-stage renal disease (Blumenthal 2006). Renal scarring associated with VUR has been shown to account for 25% of all end-stage renal disease in children and young adults (Smellie, Barratt et al. 2001). In an unselected population of VUR patients treated in Helsinki during childhood in 1955-1965, 11% had died of kidney-related conditions or had developed ESRD in adulthood (Lahdes-Vasama, Niskanen et al. 2006). However, Salo et al. in their recent paper



(Salo, Ikäheimo et al. 2011) pointed out, that recurrent childhood UTIs without structural kidney anomalies play only a small, less than 1%, role as a cause of CKD. The authors did not consider VUR as a structural anomaly.

### 1.5.3 Normal resolution of VUR

VUR has a tendency to resolve spontaneously in time, the resolution rate being dependent on the patient's age, gender and ethnic background, the grade and laterality of VUR, lower urinary tract function and the level of renal damage. There are papers reporting an annual resolution rate of 28% (Connolly, Treves et al. 1996), while others have reported 4% resolution (Skoog, Peters et al. 2010). Silva et al. (2006) reported a 20% resolution rate over 5 years in grade IV or V VUR patients and a 55% resolution rate at lower grades while their multivariate analysis showed the independent predictive factors for resolution of VUR to be non-white race, low-grade VUR, absence of renal scarring and lower urinary tract dysfunction. Estrada et al. (2009) found the factors predicting earlier resolution to be unilateral reflux, age less than 1 year, a low grade of VUR and a diagnosis made on prenatal hydronephrosis or sibling screening. VUR resolved during the 2 years of follow-up in 51% of their patients.

## 1.6 Diagnosis of VUR

### 1.6.1 Imaging

The most frequently used and widely agreed upon gold-standard method for diagnosing VUR is VCUG, as described in the International Reflux Study in Children (IRSC) in 1985 (Lebowitz, Olbing et al. 1985, Heikel, Parkkulainen 1966). In this method the bladder is catheterized, a radio-opaque contrast medium is instilled into the bladder and antero-posterior and oblique x-ray views are obtained of the bladder and kidneys. X-rays are taken both when the bladder is full and when the patient is voiding. VCUG has recently been re-evaluated (Ngo, Friedman et al. 2013) and found to fulfil its purpose in the diagnosis of VUR regardless of its invasiveness and the need to expose the patient's body to ionizing radiation.

Direct radionuclide cystography (isotope mictiocyctography), which is performed in much the same way as VCUG, has increased in popularity on account its lower level of radiation exposure. In this method the bladder is catheterized and filled with a radionuclide isotope, usually Tc-99m (instead of the radio opaque contrast medium). A further alternative is indirect radionuclide cystography, which complements a renogram. In this case an isotope (preferably MAG3) is administered intravenously. In both of these radioisotope methods the imaging

is performed with a gamma camera. Both methods lack the anatomical details of VCUG, however, and cannot be used for imaging the anatomy of the lower urinary tract. Thus the International VUR Grading cannot be used with isotope imaging. The direct method is more sensitive for identifying VUR than the indirect method (Bower, Lovegrove et al. 1985, Fettich, Colarinha et al. 2003). In the latter the child is asked to void only after the isotope has accumulated in the bladder. This method is therefore limited to toilet-trained, co-operative patients (Piepsz 2002).

The use of ultrasound for diagnosing VUR was reported for the first time in 1976 by Tremewan et al. (1976), who used “time position mode” ultrasound to examine 4 patients. Since that time, ultrasound has not proven to be a sensitive enough method for the diagnosis of VUR (Scott, Matthews et al. 1991), but as the diagnosis should be based on observation of a contrast agent moving from the bladder to the ureters, contrast-enhanced ultrasound has brought added value to ultrasound diagnostics. In this form of urosonography an ultrasound contrast material, a milky suspension containing micrometre-sized air bubbles that remain stable for some minutes, is instilled into the bladder and the microbubbles are detected either by by gray-scale or Doppler ultrasound transducer. This method is sensitive and involves no ionizing radiation but its potency is user-specific and it does not eliminate the need for bladder catheterization (Ascenti, Zimbaro et al. 2003).

The term “occult VUR” has been introduced to describe situation where patient has no signs of reflux in VCUG, but has recurrent febrile UTIs. Cystography performed with positioning the instillation of contrast at the ureteral orifice (PIC cystography) during cystoscopy has shown to reveal over 90% of the “occult VUR” (Rubenstein, Maizels et al. 2003). This examination is more invasive than VCUG and needs the patients to be anesthetised limiting its use only to special occasions (Edmondson, Maizels et al. 2006).

### 1.6.2 Screening

The prevalence of VUR is 27% in siblings and 36% in offspring of VUR patients. Age at the time of screening siblings or offspring is an important factor, as a 4% annual decrease in prevalence has been reported. The prevalence of dilating VUR in siblings is 10%, with no difference in occurrence between females and males (Skoog, Peters et al. 2010). Renal abnormalities are seen in 3-11% of siblings with reflux (Hollowell 2002).

The American Urological Association (AUA) has recently published guidelines for the screening of siblings and offspring of VUR patients (Skoog, Peters et al. 2010). It recommends either observation or screening with renal ultrasound, to



be continued with VCUG if renal abnormalities are present. For the screening of patients with antenatal hydronephrosis the AUA recommends VCUG if they present with UTI or if hydronephrosis is of grade 3-4 in the Society for Fetal Urology (SFU) classification. For hydronephrosis of a lower SFU grade the recommended course is either observation or VCUG. Randomized clinical trials to determine the clinical outcomes for screened patients are lacking for the time being, and the AUA's recommendations are therefore based entirely on expert opinions. Only the recommendation to perform VCUG in patients with hydronephrosis of SFU grades 3-4 is based on a data review.

## 1.7 Management of VUR

### 1.7.1 *Indications for treatment*

The guidelines for the management of VUR tend to change as the scientific knowledge evolves. The aim when treating VUR is to reduce renal scarring secondary to ascending urinary tract infection, in order to avoid reflux nephropathy, e.g. the deterioration in renal function that can affect children with VUR. Earlier the tendency was to provide more active treatment, so that VUR was searched for vigorously and treated aggressively, but today, in the light of information from several prospective studies, the European Association of Urology (EAU), the American Urological Association (AUA) and the American Academy of Pediatrics (AAP) have all revised their guidelines (Peters, Skoog et al. 2010, Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts 2011, Tekgül, Riedmiller et al. 2012). As the trend in the management of VUR has turned towards a more conservative and expectant line, the policies are not entirely congruent, however, and the consensus opinion on the optimal management of VUR is still undergoing a process of change.

### 1.7.2 *A historical perspective on the management of VUR*

A urinary tract infection in childhood was a serious illness in the 1950's. According to Steele (1963) 18% of a group of children admitted to hospital for urinary tract infection had died and 8% had progressive renal disease after 11-20 year's follow-up periods while in the series of 242 children under 12 years of age with UTI discussed by Smellie (1966), 34% had VUR and 12% had scarred kidneys.

In recent guidelines offset out the American Urological Association (AUA) and the European Association of Urology (EAU) lower urinary tract dysfunction plays an important role in the treatment prescribed for VUR (Peters, Skoog et al. 2010, Tekgül, Riedmiller et al. 2012). This is not an entirely novel approach, however,

as DeLuca et al. (DeLuca, Swenson et al. 1962) presented a very similar approach to VUR in 1962, when they described a “habitual urinary retention” type of disorder in bladder function and emphasized bladder training and medical therapy as forming the basis for its treatment. Later, as surgical methods of treating VUR evolved, this approach became more popular and conservative means seemed to be forgotten for a while, although they have been revived recently.

The earliest publications describing attempts to reimplant the ureter date from the late 19th century, but the results were not reassuring (Dewan 2000). Hutch (1952) showed in his work in 1952 an association of renal scars, pyelonephritis and VUR in adult paraplegic patients, and he also demonstrated that the correction of VUR prevents urinary tract infections and pyelonephritis. Hutch performed his operation on patients with a neurogenic bladder, but the technique was later used for patients with primary VUR. All of the early methods (some of which are still in use) were based on the belief that almost all patients with VUR also have congenital bladder neck obstruction and for this reason the surgery was usually performed bilaterally (Dewan 2000). YV-plasty (cutting along the Y lines and closing the V lines) in the anterior part of the bladder neck was often performed in order to achieve more space at the bladder outlet and to minimize outlet obstruction.

### *1.7.3 Conservative treatment for VUR*

The resolution rate for primary VUR is good, reaching 80% in cases of low-grade VUR and 50% for high-grade VUR (Tekgül, Riedmiller et al. 2012). It is therefore reasonable to either “wait and see” or to treat VUR patients with continuous or intermittent antibiotic therapy. The goal of the treatment should be to prevent renal scarring brought about by infectious urine ascending to the kidneys. Antibiotic therapy is based on the principle that sterile reflux will not damage the kidneys as long as the lower urinary tract functions correctly. Voiding dysfunction should therefore be assessed and treated. Continuous antibiotic therapy (CAP) is continued until either VUR resolves or the child is toilet-trained and there are no signs of voiding disorders. Single low doses of antibiotics, e.g. amoxicillin, trimethoprim, trimethoprim-sulfamethoxazole, or nitrofurantoin may be used for treatment and regular follow-up visits are recommended for the assessment of kidney growth by ultrasound and the resolution of VUR by MCG (Tekgül, Riedmiller et al. 2012). In a recent Cochrane review (Nagler, Williams et al. 2011) CAP was shown to reduce renal scarring by 60% compared with untreated patients, and although no difference in the number of renal scars was detected between CAP and surgical treatment, the surgical patients experienced less febrile UTIs.

The overall prevalence of primary VUR in patients with UTI is approximately 30% (Sargent 2000). Earlier VCUG was suggested for all children after their first UTI in order to identify any underlying VUR. If VUR was diagnosed, CAP or surgery was recommended to correct it. Today the EAU recommends VCUG only for children under 2 years of age after their first febrile UTI (Tekgül, Riedmiller et al. 2012), while the AAP does not recommend VCUG after the first UTI even if it is febrile, or in children aged less than 2 years and do not advise starting CAP at that point, either (Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts 2011). Nevertheless, the AUA, operating in the same continent, strongly advises the commencement of CAP after the first febrile UTI for children aged less than one year (Peters, Skoog et al. 2010).

The assessment and treatment of voiding dysfunction is part of the conservative management of VUR. Lower urinary tract (LUT) dysfunction increases the risk of UTI and renal scarring in VUR patients, and it also lowers the resolution rate (Colen, Docimo et al. 2006). The methods for treating LUT dysfunction comprise bladder training, anticholinergic medication when needed and the treatment of constipation (Peters, Skoog et al. 2010).

Observational management, watchful waiting, has become part of the management of VUR. This means regular follow-up visits and scheduled urinary tract imaging without antibiotic therapy or operative treatment. The idea is based on the favourable spontaneous resolution rate for VUR. The best consensus regarding its use exists in the case of children over two years of age and without voiding disorders or renal scarring. No clear guidelines exist as to which patients could best be managed with observation only, or concerning the scheme of the follow-up (Peters, Skoog et al. 2010, Tekgül, Riedmiller et al. 2012).

#### *1.7.4 Surgical treatment for VUR*

The principle of the surgical treatment of VUR is to enhance the functioning of the ureterovesical valve mechanism. When the pressure inside the bladder increases during micturition, the intramural ureter is shortened, the submucous layer pushes the ureter towards the muscular backing of the bladder and the walls of the distal ureter compress together to prevent any backflow of urine. As Paquin stated in 1959, for the vesicoureteral valve to function, the ratio of the intramural length of the ureter to the ureteral diameter measured at the ureterovesical junction should be 5:1 (Paquin 1959).

All the available surgical procedures observe the same basic principles. The distal ureter is mobilized without damaging the circulation or innervation and a submucous tunnel is created that implements the 5:1 ratio mentioned above

(Paquin 1959). The mobilized distal ureter is placed in the submucous tunnel, while avoiding twisting or angulation, and anastomosed to the mucosa. The surgical procedures can be divided into intravesical and extravesical operations depending on whether they are performed inside or outside the urinary bladder. The resolution rate for operatively treated VUR is reported to be up to 99% (Nagler, Williams et al. 2011). The common adverse effect is postoperative obstruction of the urinary tract, occurring in 0-7% of patients (Jodal, Smellie et al. 2006, Birmingham Reflux Study Group 1987).

The indications for surgical treatment mentioned in recent EAU guidelines (2012) are recurrent break-through infections in patients with CAP, preferably with endoscopic subureteric injection therapy. Surgical therapy “should be considered” in patients with high-grade (IV-V) VUR, for whom open surgical correction is preferred to endoscopic therapy. In patients less than 5 years of age with dilating VUR (grades III-V) and an abnormal renal parenchyma, surgical therapy is an alternative to CAP. Endoscopic therapy can be an option for children with a lower grade of VUR whose parents prefer it to CAP (Tekgül, Riedmiller et al. 2012).

The AUA has a more conservative approach in its latest guidelines (2010), which are categorized as “standard”, “recommendations” or “options” depending on the published scientific evidence, the standard category representing the most rigid treatment policy. Open or endoscopic surgical treatment can be considered an “option” as an initial management method, as conservative methods are preferred. In cases of break-through UTI during CAP, surgical treatment is a “recommendation” (Skoog, Peters et al. 2010).

#### *1.7.4.1 Intravesical operations for VUR*

All the intravesical procedures begin in the same way. The urinary bladder is opened, the ureteral orifices are identified and the ureters are cannulated with small feeding tubes. The ureters are then mobilized from the bladder wall and wide ureters are tapered. Depending on the technique used, the ureters are neo-implanted in a new position in the bladder wall.

Hutch’s method of reimplant ureters, published in 1952, was an intravesical technique, in which the ureteral orifice was left intact and the ureter was reimplanted and left in a loop on top of the mucosa (Hutch 1952). Later he introduced an alteration to his technique, in that the mucosal layer was sewn over the reimplanted ureter (Hutch, Smith et al. 1968). Jewett then made some modifications to the technique in which he closed the detrusor under the ureter and the mucosa over the ureter (Jewett 1955).

In 1958 Politano and Leadbetter (Politano, Leadbetter 1958) introduced a procedure in which the ureter was mobilized from the bladder and then brought

back through the muscle layer in a more cranial part of the bladder, under a submucous tunnel and to a more medial point superior to the original orifice. The problem with this technique is possible kinking of the ureter when the bladder is full, causing obstruction of the distal ureter (Dewan 2000).

Cohen (1977) simplified the Politano-Leadbetter procedure to eliminate the need for extraperitoneal dissection. In his technique the ureteral course through the detrusor was left intact and only ureteral advancement was performed, creating a longer submucous tunnel and a new hiatus across the trigonal area towards the contralateral ureter. Other trigonal ureteral advancement techniques are Glenn-Anderson's and Gil-Vernet's operations. In the Glenn-Anderson technique the ureter is advanced towards the bladder neck, the operation being otherwise performed in the same manner as in Cohen's procedure (Glenn, Anderson 1967). In the open intravesical operation of Gil-Vernet (Gil-Vernet 1984), published in 1984, the area (both the mucosa and the muscular layer) between the two ureteral hiatuses was opened transversally and closed longitudinally, lengthening the submucous course of the ureters.

The Paquin technique (Paquin 1959) is a mixture of the intravesical and extravesical approaches. The ureters are dissected from the detrusor in an extravesical manner, but the implantation is made intravesically. The Paquin technique makes it possible to construct a long submucosal tunnel.

#### *1.7.4.2 Extravesical operations for VUR*

Lich (1961) and Gregoir (1964) independently described an extravesical operation for VUR in which the ureter is mobilized extravesically at the ureterovesical junction. The detrusor muscle is incised from the junction caudally and laterally, while the mucosa is left intact. In the detrusorraphy modification of the technique the ureter is anchored to the inferior part of the distal limit of the dissected detrusor and the detrusor is sewn over the ureter, creating muscular backing for the submucous tunnel. In the original technique of Lich, the bladder was opened to introduce ureteral stents, but it is more common to perform the operation entirely extravesically. The extravesical approach has been criticized on account of the postoperative voiding difficulties, which have been thought to be caused by iatrogenic damage to the innervating nerves of the bladder during detrusor dissection, as it has been shown that the pelvic plexus is located 1.5 to 2 cm dorsally and medially of the ureterovesical junction (Leissner, Allhoff et al. 2001). Voiding difficulties (reported in up to 4–15% of patients) are seen particularly in male patients with bilateral extravesical ureteral reimplantations, especially when the detrusorraphy technique is used (Barrieras, Lapointe et al. 1999).

#### 1.7.4.3 Laparoscopy

Both extravesical and intravesical operation techniques have been used for laparoscopic reimplantation of the ureter. Extravesically, the detrusor is incised, the ureter is freed and a longer submucosal tunnel is created by a modification of the Lich-Gregoir technique (Riquelme, Aranda et al. 2006), while intravesically a normal laparoscopy, also called vesicoscopy, is performed inside the bladder by either the Cohen or Glenn-Anderson method. Recovery from both kinds of operation seems to be more rapid and the results at least equal to those achieved with a conventional technique (88-100%) as far as can be judged from the limited amount of published data (Hayn, Smaldone et al. 2008). Intravesical laparoscopy has poorer results in children younger than two years of age (Riquelme, Aranda et al. 2006, Kutikov, Guzzo et al. 2006). No long-term results have yet been published.

#### 1.7.4.4 Endoscopy

Endoscopic therapy for VUR has become an alternative to open surgery. In this approach bulking agent is injected into the subureteric area to make the ureteral orifice smaller and improve the ureteral valve mechanism. The first such bulking agent to be used for the endoscopic correction of VUR, reported in 1981, was teflon (polytetrafluoroethylene, PTFE) (Matouschek 1981), and other injectable agents, such as bovine collagen, polydimethylsiloxane (a silicon product known as Macroplastique®), autologous chondrocytes and dextranomer/hyaluronic acid (Deflux®) have been used since then. The most common material at the moment is dextranomer/hyaluronic acid, which is the only injectable bulking agent to be approved by the USA Food and Drug Administration for use in the treatment of VUR. Good results (80%-90%) have been reported when treating all grades of VUR, usually with one or two injections (Capozza, Lais et al. 2004).

Relapses have also been reported. The Swedish reflux trial compared an endoscopically injected bulking agent group with a close observation group and an antibiotic prophylaxis group and found that some of the patients who had been graded as having no reflux or grade I reflux had returned to a dilating VUR category during the 2-year follow-up (Brandström, Jodal et al. 2011). Similar findings have been reported by Lee et al. (Lee, Gatti et al. 2009), who noticed after one year of injection therapy that 26% of their patients had had a reappearance of VUR, which had completely disappeared after the first injection.

## 1.8 Results of VUR treatment

Different methods of treating VUR were assessed in a recent Cochrane review (Nagler, Williams et al. 2011) by evaluating randomized controlled trials, enabling the following conclusions to be drawn. Surgical treatment of VUR reduces the incidence of febrile urinary tract infections as compared with medical treatment and it does not affect the incidence of renal scars relative to the latter. CAP therapy significantly reduces the risk of new renal scars as compared with patients receiving no treatment.

In the Birmingham Reflux Study in the 1970's and 1980's children under 15 years of age with dilating reflux were randomly allocated to either operative or conservative treatment and followed up for 5 years. The operative group underwent a Politano-Leadbetter or Cohen procedures, while the conservative group was treated with CAP. Full resolution of VUR had been achieved by 98% of the operative group patients within five years, but only 51% of those treated with CAP. No significant difference was detected in the amount of progressive renal scarring or in UTI recurrence (Birmingham Reflux Study Group 1987).

IRSC, a long prospective study set up in 1980 to assess the various methods of treating VUR drew similar conclusions to those of the Cochrane review. The study was a multicentre prospective trial, comparing medical and surgical treatment in terms of the persistence, improvement or resolution of VUR in grade III to IV patients with previous UTI aged less than 11 years at recruitment (438 patients altogether). The medical group was treated with antimicrobial prophylaxis and the surgical group with ureteral reimplantation by the Cohen or Politano-Leadbetter technique (Weiss, Tamminen-Mobius et al. 1992, Jodal, Smellie et al. 2006). The originally scheduled follow-up time was 5 years, but this was extended to 10 years in the European limb (252 patients) (Jodal, Smellie et al. 2006). During the first 5 years 40 new renal scars were detected, equally many in the surgical and medical groups (Olbing, Claesson et al. 1992), while during the last 5 years only 2 new scars were found. After 10 years of the survey there were equal frequencies of UTIs, but the medical group had more febrile infections. No difference was observed between the groups in renal function, renal growth or the number of new renal scars (Olbing, Smellie et al. 2003).

In the Swedish Reflux Trial the small children with dilating VUR of grade III or IV as detected in VCUG were divided into three groups and followed up for 2 years. The groups were 1) surgery by the endoscopic subureteric injection technique (using the dextranomer/hyaluronic acid copolymer Deflux®), 2) CAP with trimethoprim, and 3) close observation. VUR had been diagnosed during an examination for UTI in 96% of the patients, in connection with antenatal hydronephrosis in 4%. Renal scars were seen in DMSA in 61% of the patients on



enrolment (Brandström, Esbjörner et al. 2010). An abnormal voiding pattern in toilet-trained children in the follow-up was associated with a higher rate of UTIs and a lower rate of VUR resolution. Recurrent UTI and new renal scars were seen significantly less often in girls with endoscopic injection therapy and CAP groups than in observation only group after two years of follow-up. The management strategy constructed by the authors on the bases of these findings was that boys over 1 year of age with dilating reflux should be assigned to observation only, because no benefit could be gained from active surgical or medical treatment, but that girls over 1 year of age with dilating VUR should be treated either with endoscopic injection therapy or with CAP in order to avoid recurrent UTIs and renal scarring (Brandström, Esbjörner et al. 2010, Sillén, Brandström et al. 2010, Brandström, Nevéus et al. 2010, Brandström, Jodal et al. 2011).

## 1.9 The long-term outcome of VUR

Many of the long-term follow-up studies present results applying to patients whose initial treatment had started in the 1960's or 1970's (Brakeman 2008), which implies that their VUR was managed according to different treatment protocols from those used at present. Many of the papers also show a selection bias towards more severe VUR and renal scarring, which should be borne in mind when interpreting the results.

There are several publications dealing with the long-term follow-up of VUR patients, and these vary widely in the selection of the original patient populations and the treatments given. Smellie (1998) and her colleagues reported a cohort of patients followed up in the UK from presentation to adulthood, all of whom had UTI and VUR at referral and were treated medically or operatively (15%). The mean ages were 5 years at presentation and 27 years when examined in adulthood. The follow-up times were in the range 10-35 years. 148 of the initial 226 patients (65%) attended the adult investigations. The frequencies of UTIs, hypertension and radiologically observable renal scarring were reported, as were renal function and pregnancy outcome.

Köhler et al. (2003) studied 115 Swedish patients who had been diagnosed with VUR in adulthood, assessing in particular hypertension, renal function and pregnancy outcomes. Likewise Mor et al. (2003) investigated the long-term outcomes for 322 patients treated operatively for VUR at a mean age of 6 years in Israel and followed up for 20-30 years, 31% of whom attended the adult investigations, in which renal function, hypertension, the frequency of UTIs and pregnancy outcomes were assessed. Jacobson et al. (1989) reported long-term results in a group of 30 Swedish patients with renal scarring and UTI, 70% of whom had had VUR during childhood. The mean age at diagnosis was 6 and the



average follow-up time 27 years. Again, renal function, hypertension, the frequency of UTIs and pregnancy problems were assessed. Lahdes-Vasama et al. (2006) looked more closely at 127 patients out of a cohort of 267 Finnish childhood VUR patients treated either operatively (34%) or conservatively, with a mean follow-up time of 37 years, paying attention to renal function, the frequency of hypertension and renal scars detectable by ultrasound. Silva et al. (2006) studied a cohort of 735 patients in Brazil with childhood VUR diagnosed at a mean age of 2.3 years. 55% of whom were followed up more than 5 years and assessed the rate of VUR resolution and frequencies of UTI, hypertension and renal damage. The ItalKid Project is a register of pediatric patients with a deterioration in renal function, which was started in Italy in 1990. The patients included must be less than 20 years of age and have a renal function of less than 75 ml/min/1.73 m<sup>2</sup>. The register had 1348 entries by the end of 2001 (Ardissino, Daccò et al. 2003).

### *1.9.1 Urinary tract infections in earlier VUR patients*

Patients with earlier VUR are at risk of recurrent and febrile UTIs. The frequency of recurrent UTIs among patients with VUR during childhood was 57% in Jacobson's series of patients with renal scarring and UTI during childhood (Jacobson, Hansson et al. 1999), while Smellie et al. (1998) found UTIs in 31% of their childhood VUR patients, but only 2% had recurrent UTIs and 8% febrile UTIs. The rate of UTIs was 43% reported by Mor et al. in operatively treated patients with childhood VUR, while recurrent UTIs with at least one febrile episode were seen in 21% of cases (Mor, Leibovitch et al. 2003).

### *1.9.2 Kidney function and renal scarring in earlier VUR patients*

Renal scarring may lead to reflux nephropathy, proteinuria and hypertension. A small proportion of patients with reflux nephropathy end up with ESRD and kidney transplantation. Brakeman (2008) estimated recently on the basis of the United States Renal Data System and the North American Pediatric Renal Trials and Collaborative Studies registers that the incidence of ESRD related to VUR is approximately 0.7 per million patients and that of reflux nephropathy 14.8 per million in children less than 18 years of age. Patients with high-grade VUR, diminished renal function or severe renal scarring run a higher risk of ESRD (Brakeman 2008).

Jacobsson et al. found ESRD in adulthood in 10% of their patients with UTI and renal scarring in childhood and detected a progression in renal scarring in one third of the kidneys. The patients also had a lower GFR (mean 90 ml/min/1.73

m<sup>2</sup>) than the healthy controls (mean 108 ml/min/1.73 m<sup>2</sup>). (Jacobson, Eklof et al. 1989) Lahdes-Vasama et al. found abnormal GFR values (<90 ml/min/1.73 m<sup>2</sup>) in 67% of their adult patients treated for VUR as children and end-stage renal disease in 7% (Lahdes-Vasama, Niskanen et al. 2006).

VUR patients accounted for 25.4% of the cases recorded in the ItalKid register and the authors calculated the estimated risk of ESRD in this population of patients with childhood VUR and lowered renal function by the age of 20 years to be 56%. A poor renal outcome becomes noticeable during or soon after puberty. Patients with renal function less than 40 ml/min/1.73 m<sup>2</sup> have a 4 times greater risk of ESRD at 20 years of age than those with renal function 40-75 ml/min/1.73 m<sup>2</sup> on entry in the register (Ardissino, Avolio et al. 2004).

### *1.9.3 Blood pressure in earlier VUR patients*

High blood pressure is a common finding in patients with earlier VUR. Jacobson found arterial hypertension in 23% of his patients with childhood UTI and renal scarring (Jacobson, Eklof et al. 1989), while Lahdes-Vasama et al. reported >+2 SD readings in either systolic or diastolic blood pressure in 28 patients, and 14 patients were receiving antihypertensive medication (Lahdes-Vasama, Niskanen et al. 2006). Köhler detected hypertension in 44% of the patients with VUR diagnosed during adulthood, but moderate to severe disease was seen only in patients with renal damage as seen in iv-uography (Köhler, Tencer et al. 2003). Silva et al. (Silva, Maria et al. 2006) found hypertension in 19% of their adult patients with earlier VUR and in 52% of the former VUR patients with CKD. Unlike the other authors, Smellie found arterial hypertension in adulthood in only 6% of her prospective cohort of patients with childhood VUR during adulthood (Smellie, Prescod et al. 1998), and Also Mor et al. likewise reported the hypertension rate in patients with operatively treated childhood VUR to be 6% (Mor, Leibovitch et al. 2003).

### *1.9.4 Lower urinary tract function in earlier VUR patients*

Lower urinary tract dysfunction and voiding disturbances are related to VUR in pediatric patients, but published data concerning adult patients with earlier VUR are lacking.

## *1.9.5 Pregnancy outcome in VUR patients*

### *1.9.5.1 Physiological changes in the urinary tract during pregnancy*

Physiological changes take place in the urinary tract during pregnancy. As the mother's total vascular volume changes, so the renal vascular and interstitial volumes increase, the total renal volume increases by up to 30% and the collecting system dilates. The renal glomerular filtration rate (GFR) and protein and albumin excretion also increase (Jeyabalan, Lain 2007, Macejko, Schaeffer 2007).

Reports of urodynamic results in pregnant women are contradictory. Several authors point to increased bladder capacity during pregnancy (Iosif, Ingemarsson et al. 1980, Muellner 1939), whereas others (Francis 1960) do not find any difference or find a decrease (Nel, Diedericks et al. 2001) in bladder capacity in pregnant women. There are papers showing that the functional urethral length in continent women increases during pregnancy and the closing pressure rises by an average of 12cmH<sub>2</sub>O (Iosif, Ingemarsson et al. 1980, Iosif, Ulmsten 1981, Van Geelen, Lemmens et al. 1982). Nel et al. (2001) found that 41% of their South African series had abnormal neurological findings (mostly absence of the pubocavernous reflex) during pregnancy, and this persisted in 62% of them. They also found idiopathic detrusor over-activity in 23% of the pregnant women, which was persisting after pregnancy in 67% of cases. In the urine flow measurements they found a statistically significant increase in maximum flow rate (mean 33ml/s vs. 29 ml/s) and in average flow rate (mean 16ml/ vs. 13ml/s) after pregnancy compared with measurements made during pregnancy. These changes predispose women to urological problems during pregnancy.

### *1.9.5.2 Complications during pregnancy*

Although increased urinary frequency is commonly experienced (43-65%) during pregnancy (Nel, Diedericks et al. 2001, Stanton, Kerr-Wilson et al. 1980), the reason for it is debatable, possible factors being increased volume of uterus, increased GFR and increased fluid intake and urine output. Other lower urinary tract symptoms frequently complained of during pregnancy are urgency (27-71%) and nocturia (34-87%) (FitzGerald, Graziano 2007, Nel, Diedericks et al. 2001). All these symptoms are usually present already in the first trimester, increase during pregnancy and return to pre-pregnancy levels post-partum (FitzGerald, Graziano 2007). Urinary retention is a rare problem during pregnancy (1/3000), and is seen more often in women with a retroverted uterus. High levels of progesterone have also been associated with urinary retention, even in non-pregnant women with assisted reproductive technology. Both stress and urgency incontinence are frequent in pregnancy, their prevalence being as high as 41% and 20%,

respectively (Stanton, Kerr-Wilson et al. 1980). The highest prevalence is in the third trimester. Unlike urgency, frequency and nocturia, stress and urgency incontinence often persist postpartum (FitzGerald, Graziano 2007), although Nel et al. (2001) found stress incontinence in 11% of their indigenous South African population during pregnancy but none afterwards. This may be due to the different population group.

The prevalence of urinary tract infection in healthy women during pregnancy has been reported to be 1-18% and that of non-symptomatic bacteriuria 1-9% (Nel, Diedericks et al. 2001, Macejko, Schaeffer 2007). Both maternal and fetal complications have been associated with pyelonephritis. Before the time of antimicrobial therapy 20–50% of babies born to mothers with pyelonephritis were premature (Macejko, Schaeffer 2007). Also, approximately 6-15% of pregnancies are complicated by hypertensive disorders, while the incidence of pre-eclampsia in healthy women has been estimated to be 5-10% (Gifford, August et al. 2000, Hauth, Ewell et al. 2000). A recent register-based publication has indicated that the miscarriage rate in Denmark is 13.5% (Nybo Andersen, Wohlfahrt et al. 2000).

#### *1.9.5.3 Pregnancy complications in patients with earlier VUR*

The same difficulties apply to pregnancy outcome studies as to all long-term assessments: there may be selection bias towards more severe VUR and therefore a worse outcome than there would be among patients treated with present-day protocols.

Austenfeld and Snow (1988) evaluated 30 patients who had been operated on for VUR a minimum of 15 years before and found that 57 % had had one or more UTIs during pregnancy and 5% had had pyelonephritis. Eight spontaneous abortions were reported. Mansfeld et al. (1995) followed up a group of 62 women who had been operated on for primary VUR and 21 who had been treated non-operatively for it, observing that 65% of the operative patients and 15% of the non-operative patients had urinary tract infections during pregnancy. In both groups about 15% of the pregnancies terminated in spontaneous abortion. Also Cooper and Atwell (1993) found a marked increase (37%) in UTI frequency during pregnancy in former VUR patients with a history of operative treatment. The frequency of gestational hypertension in their series was 4%. Bukowski et al. (1998), reporting on 227 women with operative treatment for VUR, found that 41 of the 122 patients reached had been pregnant and 23% had a UTI during pregnancy. 17% of the pregnancies had terminated in spontaneous abortion. Bukowski et al. did not find any association between pyelonephritis and fetal morbidity or the frequency of spontaneous abortions, whereas Köhler et al. (2003) found that 15% of their patients diagnosed with VUR after 16 years of age had

a pregnancy that terminated in spontaneous abortion. Pre-eclampsia occurred in 10% of the pregnancies (in 18% of the mothers). Jacobson et al. (1989) found recurrent UTIs in 19% of their 21 patients with childhood UTI and renal scarring, pre-eclampsia in 13% and proteinuria during pregnancy in 25%, while Mor et al. (2003) reported a 28% rate for UTIs during pregnancy and 7% for pre-eclampsia and 9% for spontaneous abortions in 47 women who had been pregnant out of the 100 reached in a total cohort of 322 operatively treated VUR patients.

## 2 Aims of the study

The general goal of this work was to evaluate the long-term consequences of childhood VUR in middle age.

The specific aims were:

- (1) to assess lower urinary tract symptoms, abnormalities in voiding patterns and the frequency of urinary tract infections in patients with earlier VUR,
- (2) to further investigate the characteristics of lower urinary tract dysfunction in VUR patients,
- (3) to evaluate the relationship between renal size measured by ultrasound and renal function in patients with childhood VUR, and
- (4) to assess the course of pregnancy and the maternal and fetal risks involved in patients with earlier VUR.

## 3 Patients, controls and methods

### 3.1 Patients and controls

270 consecutive patients (57 men) who had been diagnosed with primary VUR without outflow obstruction or neurological pathology at Helsinki University Central Hospital (HUCS) between 1955 and 1965 were identified as eligible for the study. Of these, 23 patients had died in the meantime (12 of kidney-related conditions) and 8 had end-stage renal disease and were thus not invited. Of all the patients reached and invited, 137 (15 men) responded. The median follow-up time was 36.7 years (range, 14-48 years).

VUR was graded as non-dilating or dilating, with the non-dilating cases comprising those with grades I-II in the international grading of VUR and the dilating cases grades III-V. 90 patients had dilating VUR in either or both side. All of the patients had been primarily diagnosed with febrile UTI(s), so that VUR had been diagnosed when examining the cause of UTI. The patients had been treated either with prophylactic antibiotic therapy or operatively (50 patients). There were no definite indications for operative treatment, but it was usually the most severe cases that were operated on. The operative treatment was ureteral neoimplantation, which was performed intravesically in 49 patients and extravesically in two patients. One patient had extravesical neoimplantation performed on the left side and intravesical operation on the right side. There were 25 patients with bilateral neoimplantation. The diagnosis of VUR was initially reached in the basis of VCUG.

Patients who had been operated on with bladder neck plasty were excluded from the analysis in paper I, as the bladder neck operation could have caused a distortion in the urine flow results. The same population of patients was evaluated further in paper II, except that only women were included because of the small number of male patients. Since paper III was designed to estimate the relation between kidney size and kidney function, 2 patients with rudimental kidneys, 2 with kidney agenesis and 2 with double system kidneys were excluded in order to avoid a systematic error in the kidney size data. The purpose of paper IV was to assess the influence of VUR on pregnancies in primiparous and multiparous women. Flow-charts for these analyses are presented in Table 1.

Table 1.  
Numbers of participating patients in each paper

Paper	Consecutive patients	Died/end stage renal disease	Invited	Participated
VUR Flow	270	23 / 8	194	121
VUR Urodyn	213 females	14 / 7	150	1 <sup>st</sup> part: 114 2 <sup>nd</sup> part: 29*
VUR UÄ	252	23 / 8	185	123
VUR Gyn	213 females	14 / 7	150	87
(Renal Function)	267	23 / 8	191	127
* 1 <sup>st</sup> part of the paper 2 included urine sample, urine flowmetry and questionnaire for lower urinary tract symptoms. 2 <sup>nd</sup> part of the paper 2 women with abnormal flow and those with severe lower urinary tract symptoms participated the urodynamic study.				

The control group consisted of 43 age-matched hospital staff members (37 women and 6 men) who underwent urine flowmetry, were interviewed and filled in the same symptoms questionnaire concerning voiding symptoms as the patients. These patients served as a control group in papers 1 and 2. 20 women had been pregnant and served as a control group in paper 4.

## 3.2 Methods

### 3.2.1 Examinations and characteristics of the patients during childhood

All the patients had been treated for VUR at Helsinki University Hospital in the period 1955-1965. Their average age at diagnosis had been 4 years (3 months-12 years), and they had all been primarily diagnosed with at least one febrile urinary tract infection on the basis of a VCUG and urogram. VUR was graded as dilating or non-dilating, where dilating refers to grades III-V in the international grading system (Heikel, Parkkulainen 1966). The patients had been treated operatively or



conservatively with antibiotic medication. The intravesical operations performed were the Hutch and submucous tunnel techniques (Hutch 1952) in which the detrusor was opened or the Politano-Leadbetter (Politano, Leadbetter 1958), Williams and advancement techniques where the detrusor was left intact. The extravesical procedures performed were a modified Lich-Gregoir method (Lich, Davis et al. 1961, Gregoir 1964), performed with a detrusor opening technique or by a method in which the detrusor was not opened but its layer was “wrapped” around the ureter. The operative technique had often been a “modification” of one of those described above. The patient characteristics are shown in Table 2.

Table 2.  
Baseline characteristics of the patients

Age at diagnosis, median (range)	3 years (0.1–16)
Follow-up time, median (range)	37 years (14–48)
Dilating VUR, n	91 (66%)
Surgical treatment, n	50 (37%)
Age at the time of surgery, median (range)	4.5 years (0.1–25)

### 3.2.2 Examinations during adulthood

#### 3.2.2.1 Retrospective data collection

The diagnosis and the treatment given, operative technique and imaging results were assessed from the patient histories recorded during childhood. The case histories of patients’ pregnancies were also consulted.

#### 3.2.2.2 Interview and voiding symptoms questionnaire

The patients were interviewed concerning their general health, medication and the operative treatment they had received. Their voiding symptoms were assessed by means of a questionnaire filled in during the interview (Roihuvuo-Leskinen, Koskimäki et al. 2008).

Table 3.  
Voiding symptoms questionnaire used in the research (Roihuvuo-Leskinen, Koskimäki et al. 2008).

How many times do you have to urinate during day and night?

Daytime \_\_\_ times

Night time \_\_\_ times

Do you need to hurry to visit the toilet? Yes \_\_\_ No \_\_\_

If yes, how often?

At least \_\_\_ times a day

At least \_\_\_ times a week

More seldom \_\_\_

If you are visiting the toilet in a hurry, do you wet your pants? Yes \_\_\_ No \_\_\_

If yes, how often?

At least \_\_\_ times a day

At least \_\_\_ times a week

More seldom \_\_\_

Do your pants get wet when you are straining? Yes \_\_\_ No \_\_\_

If yes, how often?

At least \_\_\_ times a day

At least \_\_\_ times a week

More seldom \_\_\_

If your pants do get wet please describe the quantity.

\_\_\_ Drops

\_\_\_ Spot

\_\_\_ Very wet

### 3.2.2.3 Laboratory tests and physical examination

Several blood and urine samples were taken from the patients for laboratory testing of blood haemoglobin and serum creatinine total protein, albumin excretion in relation to creatinine excretion in the urine samples and urine bacterial cultures. Height, weight and blood pressure were also measured. Glomerular impairment was assessed from the ratio of albumin and protein to creatinine in urine samples (reference values <3.0 mg/mmol creatinine and <20 mg/mmol creatinine, respectively) (Elises, Griffiths et al. 1988). Glomerular filtration rate (GFR) was calculated indirectly by the Modification in Diet in Renal Disease

(MDRD) method (Levey, Bosch et al. 1999). Patients with GFR values 30 to 60 mL/min/1.73 m<sup>2</sup>, were considered to have moderately impaired renal function and those with less than 15 mL/min/1.73 m<sup>2</sup> were considered to have ESRD (Hogg, Furth et al. 2003).

#### 3.2.2.4 *Free flowmetry*

All the patients underwent a flowmetry with a spinning disc transducer (Dantec®, Dantec Electronics Ltd, Denmark), and residual urine was measured ultrasonographically by a urotherapist. The urine flow curves were classified in-to 5 groups, classification made by the research group of the papers 1 and 2: (1) “normal”, a bell-shaped curve in which the maximum flow rate settles between the 5<sup>th</sup> and 95<sup>th</sup> percentile in the Liverpool nomogram (Haylen, Parys et al. 1990), (2) “tower”, a high, narrow curve with its height double its width on a 50ml/min scale and a maximum flow rate exceeding the 90<sup>th</sup> percentile in the Liverpool nomogram, (3) “weak”, an elongated or plateau-shaped curve in which the maximum flow rate does not reach the 5<sup>th</sup> percentile in the Liverpool nomograms, (4) “interrupted”, a fractionated flow curve, and (5) “big bladder”, a continuous flow curve denoting a bladder capacity over 800ml.

#### 3.2.2.5 *Pressure-flow urodynamic examination*

A conventional urodynamic examination employing artificial filling cystometry and pressure flow measurement was performed by a standardized urodynamic technique (Abrams, Cardozo et al. 2003, Abrams, Blaivas et al. 1988). In the filling cystometry (Dantec®, Menuet) the bladder was filled with water at room temperature at a rate of 50ml/sec in a supine position. The patients were asked to cough after every 100ml filling of the bladder to provoke the detrusor contraction. Micturition took place in a sitting position. A two-lumen 6 Fr catheter inserted transurethrally was used to measure the pressure in the bladder and an open, fluid-filled catheter in the rectum was used to measure abdominal pressure. Pelvic floor muscle activity was recorded by means of surface electromyography (EMG) electrodes for which electrocardiography sticker electrodes were used. The Brown and Wickham infusion method was used to measure the urethral pressure profile (UPP) (Brown, Wickham 1969, Lose, Griffiths et al. 2002).

The bladder sensitivity during filling phase of the cystometry was defined decreased if the first sensation corresponded to over 40% of the bladder capacity (Malone-Lee J. 1994). Unstable detrusor contractions  $\geq 15$  cmH<sub>2</sub>O were considered as detrusor overactivity during the filling phase (Abrams, Blaivas et al. 1988) and less than 15cmH<sub>2</sub>O at maximum normal capacity was considered as normal compliance (Stephenson 1994). Bladder capacity, measured from the volume of

urine voided during cystometry and the catheterized residual urine over 800ml was considered as “big bladder”.

### 3.2.2.6 Kidney ultrasound

Kidney ultrasound examinations were performed on all the patients. The kidney dimensions were measured by an experienced radiologist using 2-dimensional sonography performed with an ATL 5000 device (Advanced Technology Laboratory, 1998) using a convex C5-2 MHz probe (69 patients), ATL 3000 (1996) using a C7-4 MHz convex probe and P2-3 phased array probes (42 patients) or an Acuson 128XP/10M device (1993) (12 patients). Nine dimensions per kidney were measured twice and the mean values were recorded (Figure 3). The length, width and antero-posterior diameter of each kidney were measured and its volume was calculated using an ellipsoid formula: length x width x AP diameter x 0.52 (Bartrum, Smith et al. 1974). The kidney volume was divided by the body surface area as calculated by the Mosteller method (Mosteller 1987) to exclude the effect of the patient's size and to achieve a normalized kidney volume. A small kidney was defined as one that was 80% or less of the mean renal volume in the population concerned. As all patients had had VUR, the refluxing kidneys were compared to those kidneys without VUR.

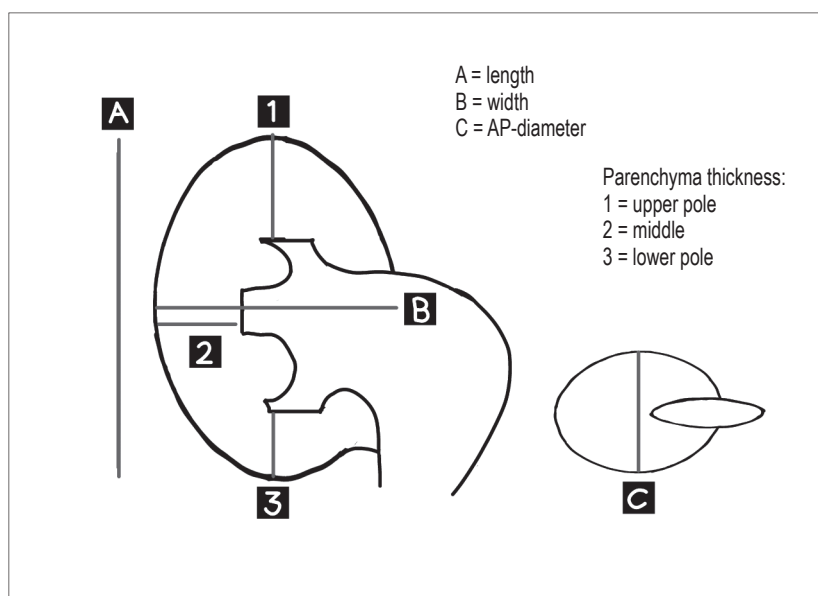


Figure 3.  
Kidney ultrasound measurements. A kidney length, B kidney width, C kidney AP-diameter, 1 upper pole width, 2 parenchymal thickness, 3 lower pole width.

### 3.2.3 Terminology

“The methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted.” (Abrams, Cardozo et al. 2003)

### 3.2.4 Statistical methods

The statistical analyses were performed with the Microsoft Excel, StatisticXL and SPSS software packages. Student's t-test was used to assess the significance of normally distributed continuous variables and the Mann Whitney U-test for those with a skewed distribution. The chi squared test and Fisher's exact test were used with categorical variables. Pearson's correlation coefficients were used when comparing normally distributed continuous variables, and multivariate regression logistic analyses when examining relationships between several categorical values. P values less than 0.05 were considered statistically significant.

### 3.2.5 Ethical considerations

The protocol for this work was approved by the ethical committees of HUUS and Tampere University Hospital.

## 4 Results

### 4.1 Lower urinary tract dysfunction

Lower urinary tract (LUT) dysfunction and symptoms and the frequency of urinary tract infections were assessed in middle-aged patients with childhood VUR and compared with findings in an age-matched control group. 53% of the patients complained of one or more of the following voiding symptoms: urgency, frequency (8 or more daytime voidings), urgency incontinence or stress urinary incontinence, 20% of the patients and 11% of the controls ( $p=ns$ ) experienced urgency incontinence, 31% of the patients reported urgency or urgency incontinence, 48 patients (40%) had either stress or urgency incontinence, and 34% of the patients and 16% of the controls ( $p<0.05$ ) had stress urinary incontinence (SUI). 40% of the primiparous or multiparous women and 29% of the nulliparous women reported SUI,  $p=ns$ .

Urine flowmetry showed 40% of the patients with childhood VUR to have abnormal flow, which was also the case with 41% of the patients with urgency incontinence and 37% of those with stress urinary incontinence. The abnormal curve was most often either tower shaped or interrupted in both of the groups. 97% of the controls had a normal flow curve shape. The patients who had been operated on for VUR in childhood had an abnormal curve shape more often (55%) than did the patients who had been treated conservatively (30%,  $p<0.05$ ), most often with “interrupted” or “weak” flow (see Table 1). 55% of the patients with bilateral dilating VUR in childhood had “interrupted” flow, while 19% had “normal” flow ( $p<0.05$ ). The male patients had a “weak” flow twice as often as did their controls (7 of 11 and 1 of 6,  $p=ns$ ), while the rest of the male patients and their controls had a “normal” flow.

Table 4.

Percentages of uroflow patterns among 46 surgical and 83 non-surgical patients

Females & males	Total % (n)	Normal	Big bladder	Tower	Weak	Interrupted
Surgical	100 (44)	45 (20)	7 (3)	2 (1)	27 (12)	18 (8)
Non-surgical	100 (76)	70 (53)	8 (6)	9 (7)	12 (9)	1 (1)

## 4.2 Urodynamic findings

To investigate the voiding disorders more intensively the patients with an abnormal urine flow curve or with severe voiding problems were invited to enter the second part of the urodynamic study. 19 women with abnormal flowmetry (out of 27 such patients) underwent these urodynamic examinations, together with 10 women who had normal free flow but suffered from urinary symptoms. 18 of the 29 patients who entered the urodynamic examinations had had operative treatment for VUR during childhood.

16 of the 29 (55%) patients examined in the urodynamic part of the study had lower urinary tract symptoms, eight reported suffering from urgency incontinence and 6 of these also from SUI. 14 patients suffered from SUI. The patients with LUT symptoms had an interrupted or normal shaped urine flow curve more often than any other curve shape.

The urodynamic tests showed 12 out of the 29 patients to have decreased bladder sensitivity during filling phase. This frequency was not affected by the treatment modality or VUR grading. Bladder capacity, measured from the volume of urine voided during cystometry and the catheterized residual urine, was over 800ml in 30% of the patients. One patient had detrusor overactivity during the filling phase, a “weak” flow in flowmetry and urgency incontinence, while decreased compliance during filling phase was detected in 3 patients, all of whom had a “weak” flow and two of whom had SUI. Provocation test (coughing), however, during filling did not reveal any detrusor overactivity.

Abnormal sphincteric EMG activity (Abrams, Blaivas et al. 1988) was detected in 70% of the patients, including 89% of those with an “interrupted” flow curve shape. All the patients with childhood bilateral dilating VUR had abnormal sphincteric EMG activity, while the frequency in the other patients was 47% ( $p < 0.05$ ). The treatment modality did not affect the frequency of EMG

Table 5.  
Abnormal findings during the filling phase

Free flow pattern	Normal	Big bladder	Tower	Weak	Interrupted	Total
Number of patients	10	2	2	6	9	29
FS > 40% of BC	5	1	0	3	3	12
Overactive detrusor	0	0	0	1	0	1
Decreased compliance*	0	0	0	3	0	3
*Pdet $\geq$ 15 cmH <sub>2</sub> O (Abrams, Blaivas et al. 1988)						

activity. 91% of the patients with frequent recurrent UTIs (more than once a year) in adulthood had sphincteric EMG activity, as compared to 56% of those who had them less frequently or not at all ( $p<0.05$ ). The patients with abnormal sphincteric EMG activity did not have renal scars any more often than those with normal EMG activity (85% and 89%, respectively,  $p=ns$ ).

### 4.3 Urinary tract infections

UTIs were reported in 76% of all the patients with childhood VUR and in 57% of the controls ( $p<0.05$ ). The frequency of the UTIs did not seem to be affected by the bladder capacity or the amount of residual urine. Frequent UTIs, more than one infection per year, were reported by 25% of the patients but none of the controls ( $p<0.05$ ). In all the flow groups except for the “tower” group the ratio of patients with UTIs to patients with no infections was at least 2:1, whereas that in “tower” group was 1:3, i.e. 75% of the patients with a tower-shaped curve had not had any UTIs. Neither the male patients nor their controls had had any UTIs.

80% of the 29 patients with abnormal flow or normal flow but LUT symptoms had had one or more UTI during adult life and 38% more than once a year. In the control group, 57% of the subjects had had infections during adult life but none of them yearly ( $p<0.05$  in both, when comparing the frequencies of UTIs and yearly UTIs between the patients and the controls).

### 4.4 Ultrasound measurements of kidney size and function

The kidneys affected by VUR in childhood were on average 12% smaller in size when measured by ultrasound than those unaffected by VUR, and 16% smaller if affected by dilating rather than non-dilating VUR ( $p<0.05$  in both cases). The patients with a VUR diagnosis before 2 years of age (normalized total volume 118 mL) had on average smaller kidneys in ultrasound ( $p<0.05$ ) than those with a diagnosis after 2 years of age (normalized total volume 137mL).

13% of the patients with childhood VUR had a moderate deterioration in kidney function, defined as a GFR less than 60 mL/min/1.73 m<sup>2</sup>. The patients with either bilateral or unilateral small kidneys had a reduced GFR more often (in 22% of cases), than did those with normal-sized kidneys (5%,  $p=0.008$ ). The correlation with GFR and the body surface-normalized total kidney volume was moderate (Pearson's  $r=0.42$ ,  $p=10^{-6}$ ).

Patients with two small kidneys more often had hypertension (in 50%) and proteinuria (in 25%) than those with one small kidney (27% and 14%, respectively) or those with two normal-sized kidneys (36% and 16%), although the differences between the groups were not statistically significant. There was no



increased rate of hypertension or proteinuria in patients with a thin upper pole parenchyma. Multivariate regression analysis showed the risk of proteinuria to be threefold in those patients with renal scars and a small kidney relative to those without scarring and with normal-sized kidneys (OR=3.1,  $p<0.05$ ).

## 4.5 Pregnancy outcome in patients with childhood VUR

59% of the mothers with childhood VUR had experienced maternal complications during pregnancy (hypertension, pre-eclampsia, miscarriages or UTIs), these being seen more often in patients who had been operated on and whose disease had been more severe. 37 of the 55 patients with dilating VUR in childhood had maternal complications, as compared with the 14 of the 43 non-dilating VUR ( $p<0.05$ ). Similarly the mothers who had renal scars in middle age (48 patients) and those with frequent UTIs during adult life (28 patients) had maternal complications more often during pregnancy (63% and 31%, respectively) than those without scars (42%) or infections (21%). The patients who had been diagnosed with proteinuria in dipstick tests during pregnancy more often had gestational hypertension (44% vs. 15%) and UTIs (55% vs. 23%) during pregnancy than those without proteinuria ( $p=0.006$  for both.) The patients with interrupted or weak urine flow did not have higher incidence of complications during pregnancy (Table 6).

Miscarriages were reported by 23% of the women, comprising 30 spontaneous abortions before 20 weeks of gestation and 3 after 20 weeks of gestation. Renal scarring or the occurrence of UTIs during pregnancy did not affect the miscarriage rate. 25% of the women who had had operative treatment for VUR during childhood had spontaneous abortions, as compared with 22% of those with conservative treatment. There were 7 mothers out of 20 controls with spontaneous abortions.

UTIs were seen in 33% of the mothers during pregnancy and 4 out of every 5 of these had had dilating VUR in childhood while 38% had been operated on for VUR. 42% of the mothers who had had dilating VUR during childhood had UTI(s) during pregnancy as compared with 19% of those who had had non-dilating VUR ( $p<0.05$ ). Controls had not experienced UTIs during pregnancy.

The incidence of fetal complications, including intrauterine growth retardation, preterm infants and birth weight less than 2500g, was 30%. In 63% of the women with complications during pregnancy renal scars were detected later in middle age, but the rate of fetal complications was not increased in these women, nor was it affected by the severity of VUR during childhood, the treatment modality adopted for it, renal scarring or the number of pregnancy-related UTIs. The incidence of fetal complications in the patients with frequent UTIs during

adulthood was 50% while 22% of those who did not have frequent UTIs had fetal complications ( $p<0.05$ ).

Most of the women (70%) did not know that they had been treated for VUR during childhood, while 60% knew that they had been treated for UTI, without knowing the reason.

Table 6.  
Pregnancy complications in VUR mothers

	Maternal complication n (%)	No maternal complication n (%)	All n (%)
Mothers	54	33	87
Births	110	65	175
Operation during childhood <sup>1</sup>	21 (39)	8 (24)	29 (33)
Age at diagnosis	4.5	4.3	4.4
Dilating VUR <sup>2</sup>	36 (67)	19 (58)	55 (63)
<i>Fetal outcome</i>			
Preterm <37w	5 (9)	3 (9)	8 (9)
Very preterm <32w	1 (2)	2 (6)	3 (3)
Small <2500g <sup>1</sup>	6 (11)	1 (3)	7 (8)
IUGR	12 (22)	10 (30)	22 (25)
IUGR, small, preterm	15 (28)	11 (33)	26
<i>Findings in middle age</i>			
Renal scars <sup>3</sup>	34 (63)	14 (42)	48 (55)
Adulthood UTI >1/year <sup>4</sup>	17 (31)	7 (21)	24 (28)
GFR<60	7 (13)	3 (9)	10 (12)
Albuminuria or proteinuria <sup>4</sup>	11 (20)	3 (9)	14 (21)
Abnormal flow (I or W)	10 (19)	6 (18)	16 (18)
<sup>1</sup> p=0.2 <sup>2</sup> p=0.4 <sup>3</sup> p=0.08 <sup>4</sup> p=0.3 Maternal complication= gestational hypertension, proteinuria, pre-eclampsia, difficulties in conceiving, spontaneous abortions IUGR Intrauterine growth retardation MDRD estimated glomerular filtration rate			

## 5 Discussion

This thesis reports on the long-term outcome for childhood VUR patients treated at Helsinki University Central Hospital, focusing especially on urological findings. This cohort of patients had an increased incidence of abnormal findings in uroflow measurements, urodynamic examinations and kidney function and volume measurements during adulthood compared with healthy controls. This was especially true of the patients who had been treated operatively during childhood. Other problems, such as an increased rate of pregnancy complications, accumulated mainly in those patients with renal scarring, which is in line with earlier reports.

No long term results regarding voiding symptoms and urodynamic findings or results concerning kidney volumes and function in VUR patients have been published previously.

Although this is a consecutive series of VUR patients, there may be some selection bias towards more severe disease. Renal scarring at the time of VUR diagnosis was assessed in these patients by intravenous pyelography, which is less sensitive than the DMSA method used today and led to the discovery of only the gravest scars. The patients were treated at Helsinki University Hospital, where in general the most severe cases are taken care of and thus probably only the most severely ill patients with recurrent febrile UTIs were diagnosed and the less severe cases were never recorded as having suffered from VUR. Silva et al. having collected a retrospective cohort of VUR patients from the years 1970-2004, found that the probability of CKD in patients diagnosed after 1990 was 2% compared with a prognosis of 5% in those diagnosed before 1990 (Silva, Maria et al. 2006). This retrospective study entails the same methodological disadvantages. The control group was not examined with kidney ultrasound which was an unfortunate shortcoming of the work 3, the reason being that controls were initially examined for urological symptoms and uroflow purposes.

### 5.1 Lower urinary tract

The relationship between lower urinary tract function and VUR in pediatric populations has been well proved (Koff, Wagner et al. 1998, Ural, Ulman et al. 2008). LUT function or symptoms have not been reported before in long term studies

of adult patients with earlier VUR, although it is possible that childhood bladder problems may continue in adulthood. Of the two main categories of voiding abnormalities in children, overactive bladder and dysfunctional voiding, the latter has been connected with a more severe outcome in cases of VUR (Sillen 2008). Voiding dysfunction has been reported in up to 68% of children with VUR, the usual frequency being in the range 20-50% (Sillen 2008).

We assessed LUT symptoms in patients with childhood VUR by means of a questionnaire administered as part of a patient interview. Unfortunately, no validated questionnaire suitable for women was not available at the time and therefore a non-validated form was used (table 3.) (Roihuvuo-Leskinen, Koskimäki et al. 2008). Over half of these adult patients with childhood VUR reported LUT symptoms, and 40% of the patients reported suffering from incontinence. In an overactive bladder it is the storage phase that is abnormal, and it is this that has been related to incontinence and urgency. Urgency and urgency incontinence were seen in 37% of the present patients, referring to bladder irritation or overactive bladder. The prevalence of urgency incontinence in a general population of matching age was reported in a Norwegian epidemiological survey to be 7-8% (Hannestad, Rortveit et al. 2000).

The present females with earlier VUR suffered from incontinence more often than did their controls, SUI being detected in 34% of the subjects and both urgency incontinence and stress urinary incontinence being reported twice as often in the patients than in the controls. Fritel et al. (2005) reported a 15% rate of SUI in perimenopausal French women, and the SUI frequency in the present control group is in line with this observation. Vaginal childbirth can damage the structures supporting the urethral sphincter mechanism, i.e. the pelvic floor musculature, ligaments and fascia, and can affect the pudendal nerve, exposing primiparous and multiparous women to urinary incontinence, especially stress urinary incontinence (Tunn, Goldammer et al. 2006, Jung, Ahn et al. 2012). We calculated that 70% of the women considered here had given birth to at least one child. The prevalence of urgency incontinence in Finland has recently been reported to be 26% in women and 11% in men aged 18-75 years (Vaughan, Johnson II et al. 2011), which exceeds the rate in our patient series and also the rate given in the Norwegian paper (Hannestad, Rortveit et al. 2000). Unfortunately, we lack information concerning bladder function during childhood in the present patients, so that we were not able to evaluate the change in bladder function in the course of time. We can assume from other publications, however, that at least some of the patients did have some kind of voiding dysfunction but it is impossible to say on the basis of the present data and protocol whether voiding dysfunction persists into adulthood or whether it is a separate problem.

UTIs affected 76% of the patients and in 25% they had recurred annually. This finding of frequently recurrent UTIs during adulthood differs from that re-

ported by Smellie (1998), who found UTIs in 31% of her patients but only 5% of all patients who reported recurrent UTIs. All of the Smellie's patients had been treated as children following a strict protocol that included bladder training, treatment of constipation and visits to a nursing unit every 3 months. The treatment protocol used in our population did not include a systematic intervention with regard to the voiding habits, which could be one explanation for the difference in the frequency of UTIs.

It is the voiding phase that is disturbed in patients with dysfunctional voiding being manifested as an interrupted or staccato urine curve in uroflow tests. Urine flow was normal in 60% of our patients as opposed to 97% of the controls ( $p < 0.05$ ), and a staccato type of interrupted flow curve, indicating abnormal sphincteric activity and dysfunctional voiding, was seen in 7% of the patients, all of whom had been operated on for VUR during childhood. The staccato kind of uroflow curve can also be seen in patients with neurological problems as in *cauda equina* syndrome patients (Hellström, Kortelainen et al. 1986). Patients with neurogenic bladder were not included into the present cohort. Frequently recurrent UTIs in adulthood were seen most often in patients with interrupted urine flow. Of all the operatively treated patients, 55% had an abnormal flow. Neural damage related to the bilateral extravesical technique of ureteral neoimplantation has been reported to cause voiding symptoms (Barrieras, Lapointe et al. 1999). In the present series, the operation for VUR during childhood had been performed intravesically in all but two cases, and it therefore seems unlikely that surgical manipulation of the bladder could have influenced voiding function. It is true that the surgical patients more often had problems during adult life, but this may not have been caused by the operation itself but by the fact that the disease was more severe, as it was the most severe cases that were operated on. As the treatment of VUR patients in the 1950's was based on the idea that they had congenital bladder neck obstruction, bilateral reimplantation was usually performed and bladder neck dilatation with YV-plasty was often performed at the same time as the reimplantation (Dewan 2000). YV-plasty was performed in 5 patients in the present population, and they were excluded from the free flow examination. Weak flow was seen in 17% of the patients, but it was a frequent finding in male patients (64%) and was considered to represent an obstructed flow and probably caused prostate hyperplasia rather than any condition related VUR.

### 5.1.1 Urodynamic findings

We recruited the earlier VUR patients either on account of their abnormal urine flow curves or because they had LUT symptoms, even though they had normal flow. 55% of the patients had LUT symptoms. Only women were evaluated, as

urological problems in middle-aged males and females have different profiles and our aim was to assess VUR-related problems rather than prostate-related symptoms. The present males had only normal or obstructed curves, and in any case, most of the patients in the series were females, representing the gender distribution in VUR patients at large. We found that despite the high frequency of storage symptoms, overactive bladder was an infrequent finding in this selected population of patients, but dysfunctional voiding was found frequently.

Storage symptoms such as urgency and urgency incontinence are often reported (30%) and as the frequency of children with VUR having an overactive bladder is reported to be considerable, up to 75% in urodynamic examinations (Sillen 1999), we expected to find substantial amount of detrusor overactivity in these patients in our urodynamic tests. This was not the case, however, as only one patient had an overactive bladder and only three had lowered compliance in filling cystometry. We used 15cmH<sub>2</sub>O as a limit value for unstable detrusor contractions according Abrams et al. (Abrams, Blaivas et al. 1988). Later standardization reports of the ICS have not reported the exact limit value (Abrams, Cardozo et al. 2003), and it may be that if the limit value we used had been lower the amount of patients with bladder overactivity would have increased. Most of the symptomatic patients undergoing the urodynamic examination had normal or interrupted urine flow. Abnormal sensitivity of the bladder was found in 41%, most often patients with weak flow and UTIs were reported more often in these patients than in the others ( $p < 0.05$ ).

This population of selected patients with childhood VUR and either LUT dysfunction in free flowmetry or reported LUT symptoms showed a considerable frequency of abnormal sphincteric EMG activity (in 70% of cases). By contrast, Pauwels et al. (2006) did not find any abnormal EMG activity during pressure flow examinations in their population of healthy middle-aged women without LUTS, not even in those women who were straining during voiding. It may therefore be assumed that our finding reflects real sphincteric dysfunction in this group of patients and may be of the same origin as the dysfunctional voiding in children with VUR mentioned in the published literature (Koff 1992, Sillen 2008). We used surface sticker electrodes to measure the EMG, which is a method more vulnerable to artefacts but also more pleasant for the patients than needle electrodes, the gold standard for EMG recording (Gammie, Clarkson et al. 2014).

Adult patients with childhood VUR have more often lower urinary tract symptoms and findings compared to general population. UTIs are affecting vast amount of adult patients with childhood VUR and abnormal urine flow is a frequent finding in these patients. Dysfunctional voiding rather than over active bladder can be detected in urodynamic investigations in these patients. Assessing LUT symptoms and findings also in adult patients with childhood VUR may be helpful in estimating their risk of UTIs and UTI associated complications.

## 5.2 Renal size

We evaluated kidney size as measured by ultrasound in adult middle-aged patients with childhood VUR to see whether this showed any relation to kidney function. We also investigated the influence of the severity of childhood VUR severity and method of treatment on kidney size in adulthood. Renal growth deterioration in children is a common manifestation of VUR-associated renal damage (Wikstad 2000). Caione et al. (2004) evaluated DMSA-detected kidney size in children with VUR (mean age 4,3 years) and found that the refluxing kidneys were smaller than those without VUR and that small kidney size was associated with the most severe manifestations of VUR (grades IV-V), but the diagnosis before or after 2 years of follow-up was unrelated to the frequency of small kidneys. In the present work, kidney size in adulthood was influenced by childhood VUR, as the refluxing kidneys were 12% smaller in ultrasound than the kidneys without VUR during childhood. Also the severity of childhood VUR affected the kidney size, kidneys with dilating VUR during childhood being 16% smaller than those with non-dilating VUR. Patients with a VUR diagnosis made before 2 years of age had statistically significantly smaller kidneys (normalized to body surface area) than those with a diagnosis made after 2 years of age. This could be explained by the different aetiology of VUR, as it has been hypothesized that VUR in small children is associated with renal hypoplasia and that it is only in elder children that it is related to renal scarring caused by ascending infections (Blumenthal 2006).

A moderate correlation ( $r=0.42$ ) was seen between renal size as detected by ultrasound (normalized to body surface area) and GFR. Renal scars and renal growth impairment are manifestations of renal damage (Wikstad 2000), but only the most severe scars can be seen in ultrasound, as some cases of renal scarring may manifest themselves only in decreased renal size.

Ultrasound is a reasonably safe method in assessing the need and intensity of follow-up of earlier VUR patients in clinical work. If the renal size is normal in ultrasound in these patients, the probability of moderate kidney function deterioration or development of proteinuria seems to be low.

## 5.3 Pregnancy outcome

Our hypothesis was that women with childhood VUR have an increased rate of complications during pregnancy. In earlier publications particularly patients with renal scarring and a history of VUR have been reported to have complications more often during pregnancy (Köhler, Tencer et al. 2003, Smellie, Prescod et al. 1998). Some of the present women had even been advised to not to get pregnant on account of the danger of complications. Correlations have also been observed



between UTIs during pregnancy and pregnancy complications, and the frequency of pre-eclampsia and high blood pressure during pregnancy has been attributed to renal scars. The fetal outcome seem to be unaffected by the history of mothers with earlier VUR in most cohorts (Hollowell 2008, Köhler, Tencer et al. 2003). In the present work maternal complications in the form of hypertension, pre-eclampsia, miscarriages and UTIs were seen in 59% of the mothers, while fetal complications, including intrauterine growth retardation, preterm infants and birth weight less than 2500g, were reported in 30% of the pregnancies.

UTIs during pregnancy were detected in 33% of the present mothers, but in none of those in the the control group. The published rates of UTIs during pregnancy in VUR patients are in the range 15-65% in published literature (Hollowell 2008, Smellie, Prescod et al. 1998), while the mean incidence of UTI in pregnancy among patients with earlier VUR in Hollowell's review (Hollowell 2008) was 38%, which is in line with our result. The incidence of UTI during pregnancy in a general population is 1-18% (Macejko, Schaeffer 2007). We could not confirm the finding of Hollowell (Hollowell 2008) in her review of pregnancy outcomes in VUR patients that the patients with earlier operative treatment were more prone to UTIs during pregnancy. In our series the incidence of UTI during pregnancy among mothers with a history of operative treatment for VUR was 38% and that among women with conservative treatment 31%.

The incidence of miscarriages, 23%, was higher than the figures of 9-17% reported earlier (Bukowski, Betruss et al. 1998, Köhler, Tencer et al. 2003, Mor, Leibovitch et al. 2003). Austenfeld et al. reported a 27% incidence of miscarriages in patients with operatively treated VUR (Austenfeld, Snow 1988). In the present work we did not find miscarriages in the women with operative treatment any more often than in the conservatively treated subjects. The reported incidence of miscarriages in the general population is 13.5% (Nybo Andersen, Wohlfahrt et al. 2000). The incidence of mothers with miscarriages in our control group was 35%, which exceeds both the figures for general population and those for the VUR group.

The incidence of pre-eclampsia, 7%, was the same as reported by Mor et al. (Mor, Leibovitch et al. 2003) in patients with operatively treated VUR. Others, however, have reported higher frequencies, the highest, 10-18%, being associated with renal scarring (Köhler, Tencer et al. 2003, Jacobson, Hansson et al. 1999, Hollowell 2008). The incidence of pre-eclampsia in the general population is estimated to be 5-10% (Hauth, Ewell et al. 2000).

The maternal complication rate was influenced by grade of VUR experienced during childhood and the treatment modality. 67% of the mothers with dilating VUR suffered from complications during pregnancy, compared with 44% of those with non-dilating VUR ( $p<0.05$ ). The 48 women with renal scars detected by ultrasound during middle age more often had hypertension (33% vs.



13%,  $p<0.05$ ), proteinuria (40% vs. 21%,  $p=0.07$ ) and UTIs (42% vs. 23%,  $p=0.07$ ) during pregnancy than those without renal scars. As the 27 women with proteinuria during pregnancy also had a higher rate of hypertension (44% vs. 15%,  $p<0.05$ ) and UTIs (55% vs. 23%,  $p<0.05$ ) than those without proteinuria, one can assume that these subjects also had impaired renal function which predisposed them to complications. These findings are in line with earlier papers showing that women with childhood VUR and renal scarring are more prone to complications during pregnancy (Smellie, Prescod et al. 1998, Hollowell 2008, Köhler, Tencer et al. 2003).

Fetal complications, including intrauterine growth retardation, preterm infants and birth weight less than 2500g, were seen in 26 out of 87 mothers. Renal scarring, proteinuria during pregnancy or the occurrence of UTIs during pregnancy did not affect the incidence of other fetal complications, nor did the severity of VUR during childhood. This finding differs from earlier conclusions, as Smellie (Smellie, Prescod et al. 1998) found that 8 out of 9 infants weighing less than 2500g had been born to 6 mothers with renal scarring. Interestingly, the fetal complication rate was increased in the mothers with frequent adulthood UTIs compared with those without frequent UTIs (50% vs. 22%,  $p<0.05$ ). Lower urinary tract malfunction would explain the higher frequency of UTIs, but the women with abnormal flow did not have UTIs during pregnancy any more often than those with normal flow (31% vs. 34%,  $p=0.13$ ) possibly on account of the fact that 29% of the mothers had had UTI prophylaxis during pregnancy. No correlation could be shown between fetal complications and abnormal urine flow, either.

Only 30% of the present women who had been pregnant knew they had been diagnosed with VUR during childhood and had received treatment for it. This is a possibly significant finding, as if the nursing staff remain uninformed of the underlying disease, they will not be able to manage these high risk women with the close clinical follow-up they would deserve.

Women with earlier VUR did not have any increased frequency of fetal complications during pregnancy. Increased maternal complication rate was seen in the former VUR patients with renal scars and impaired renal function manifesting as gestational proteinuria. A risk of fetal complications was associated with frequent UTIs during adulthood. Pregnant mothers with earlier VUR, renal scarring and frequent UTIs should be kept under special clinical observation.

## 6 Conclusions

VUR is a common disease in childhood and a small proportion of patients are still left with end-stage renal disease and kidney transplantation. Our understanding of the disease has increased lately, however, leading to a revision of its management strategies, although there are still many unresolved questions. This long-term retrospective cohort study, in spite of suffering from the disadvantages inherent in the method, has brought us new information concerning long-term effects of VUR.

Urgency, stress urinary incontinence and abnormal urine flow are frequent findings in adult patients who have had childhood VUR, and these patients also suffer from frequent UTIs. Despite the occurrence of symptoms referring to overactive bladder, OAB is an infrequent finding in urodynamic examinations of women with abnormal flow and severe LUT symptoms. Abnormal sphincteric EMG activity, indicating dysfunctional voiding, is a frequent finding in women with childhood VUR and abnormal flow or severe LUT symptoms.

Kidneys with history of VUR, especially dilating VUR, are smaller than usual, and there is a moderate correlation between kidney size as detected by ultrasound and GFR in adult patients with childhood VUR, even though patients with small kidneys do not have an increased frequency of hypertension or proteinuria.

UTIs are a frequent finding during pregnancy in women with earlier VUR, but pregnancy complications are not increased in these patients. Women with renal scarring detected by ultrasound do have an increased rate of complication during pregnancy, however. On the other hand, the fetal complication rate is not increased by the occurrence of renal scarring or UTIs, nor by the choice of treatment modality or the severity of childhood VUR.



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## Voiding Dysfunction

# Urine Flow Curve Shapes in Adults with Earlier Vesicoureteral Reflux

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### Abstract

**Objectives and methods:** Voiding problems related to childhood vesicoureteral reflux (VUR) in a cohort of 120 patients (109 females, 11 males) were studied at early middle age (range, 33–50 yr). Forty-four patients had been operated on. The study included an interview by means of a symptom questionnaire, a urine flow measurement, a residual urine measurement, and a urine sample.

**Results:** The flow curve shape was abnormal in 40% (tower-shaped in 7%, weak in 18%, interrupted in 8%, and big bladder in 8% of patients). Forty-five percent of operated patients and 70% of nonoperated patients had a normal flow curve shape. Almost half of the operated patients (45%) had either an interrupted or a weak flow. Figures for stress incontinence and urgency incontinence among the female patients were twice those in the controls, 35% versus 16% ( $p = 0.05$ ) and 20% versus 11%, respectively. Urinary tract infections (UTIs) were diagnosed in 76% of the adult female VUR patients and in 57% of their controls ( $p = 0.041$ ). Twenty-five percent of the female VUR patients (none of the controls) reported suffering from UTI more often than once a year.

**Conclusions:** Adult patients with childhood VUR have abnormal urine flow curve shapes and UTIs significantly more often than controls ( $p = 0.00005$  and  $p = 0.04$ , respectively). Patients who were operated on for VUR especially seemed to have an interrupted or weak flow curve shape. A high percentage of these patients also suffered from urgency and stress incontinence and annual UTIs.

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## 1. Introduction

Vesicoureteral reflux (VUR) is typically diagnosed during investigation of urinary tract infection (UTI) in childhood. The general prevalence of UTI in children is 5–10% [1], and VUR is diagnosed in one third of UTI patients [2,3]. In long-term studies of VUR patients, the risk of recurrent UTIs has been estimated to be about 40% in both surgically and medically treated patients [4,5]. There is a close connection between VUR, lower urinary tract dysfunction, and UTIs in childhood. Mainly two categories of dysfunction have been found: detrusor overactivity and sphincter overactivity [6,7]. In both of these disorders, intravesical bladder pressure rises significantly, resulting in or coinciding with VUR. According to Koff and Murtagh [8], the incidence of detrusor overactivity is 55% in the reflux population. The overall incidence of the bladder dysfunction has been reported to be from 25% to 68% [9]. Most recent studies have shown that half of infants with VUR seem to have an abnormal voiding pattern, including interrupted voidings, frequent small voids, and small bladder capacity [9,10]. In other papers, however, VUR patient bladder capacity is reported to be conspicuously higher than in patients without VUR [11,12].

Although bladder function has been increasingly studied in the pediatric population with VUR, there are no published systematic analyses of adulthood voiding problems in this patient group. Neither are there reports of previous urine flow or urodynamic

studies in adult patients with earlier VUR. We aimed here to establish what kind of lower urinary tract dysfunctions, if any, could be found in earlier VUR patients. A further aim was to study the frequency of UTIs in these adult patients.

## 2. Patients and methods

The ethical review committee at Helsinki University Central Hospital (HUCS) approved this study. The material comprised 270 consecutive patients who had been diagnosed with primary nonobstructive VUR (without outflow obstruction or neurological pathology) at HUCS between 1955 and 1965. Twenty-three patients had died, and 8 with end stage kidney disease were not invited. One hundred and ninety-four invitations were sent out and 130 (67%) subjects responded. Nine patients who had undergone bladder-neck plasties (YV-plasty) were excluded because this operation could possibly have had an effect on the flow pattern. The study included interview by means of a symptoms questionnaire (Table 1), urine flow measurement, measurement of residual urine, and urine sampling. One participant could not perform an adequate urine flow measurement and was excluded from that part of the study. Also, residual urine could not be measured in one obese male patient. One female participant who voided 87 ml and had 100 ml residual urine was included. Table 2 shows the characteristics of the final study group (120 patients), including severity of VUR and the treatment given. Their VUR was diagnosed on average at the age of 4 yr (range, 3 mo–12 yr). At time of diagnosis all patients had undergone voiding cystogram and urogram studies. A “dilatating” VUR refers to grades III–V. Refluxes associated with a double system are listed separately. The following procedures for VUR were used: submucous tunnel (25), Politano-Leadbetter (10),

**Table 1 – Voiding symptoms questionnaire (questions used in study)**

How many times do you have to urinate during day and night?  
 Daytime: \_\_\_\_ times  
 Nighttime: \_\_\_\_ times

Do you need to hurry to visit the toilet? Yes \_\_\_\_ No \_\_\_\_  
 If yes, how often?  
 At least \_\_\_\_ times a day  
 At least \_\_\_\_ times a week  
 Less often \_\_\_\_

If you are visiting the toilet in a hurry, do you wet your pants? Yes \_\_\_\_ No \_\_\_\_  
 If yes, how often?  
 At least \_\_\_\_ times a day  
 At least \_\_\_\_ times a week  
 Less often \_\_\_\_

Do your pants get wet when you are straining? Yes \_\_\_\_ No \_\_\_\_  
 If yes, how often?  
 At least \_\_\_\_ times a day  
 At least \_\_\_\_ times a week  
 Less often \_\_\_\_

If your pants do get wet, please describe the quantity.  
 \_\_\_\_ Drops  
 \_\_\_\_ Spot  
 \_\_\_\_ Very wet

**Table 2 – Characteristics and flow curve shapes of all study participants**

	Patients n (%)	Flow curve shapes					Controls n (%)
	Total	Normal (%)	Big bladder (%)	Tower (%)	Weak (%)	Interrupted (%)	
Age (yr), mean (range)	41 (33–50)	41 (33–50)	41 (35–50)	41 (34–46)	40 (36–49)	38 (35–41)	39 (24–65)
Females [%]	109 (91%)	69 [63%]	9 [8%]	8 [7%]	1 [1%]	9 [8%]	37 (86%)
Males [%]	11 (9%)	4 [36%]	0 [0%]	0 [0%]	7 [64%]	0 [0%]	6 (14%)
Total	120	73	9	8	21	9	43
Bilateral VUR	63 (53%)	40 (55%)	4 (44%)	3 (38%)	10 (48%)	6 (67%)	
Dilatating VUR	75 (63%)	45 (62%)	5 (56%)	3 (38%)	16 (76%)	6 (67%)	
Bilaterally	28 (23%)	14 (19%)	2 (22%)	0 (0%)	7 (33%)	5 (56%)	
Duplex	21 (18%)	11 (15%)	1 (11%)	3 (38%)	5 (24%)	1 (11%)	
Operation for VUR	44 (37%)	20 (27%)	3 (33%)	1 (13%)	12 (57%)	9 (89%)	
Bilaterally	23 (19%)	8 (11%)	2 (22%)	0 (0%)	8 (38%)	5 (56%)	
Reop for VUR/postop obst	7 (6%)	2 (3%)	0 (0%)	0 (0%)	3 (14%)	2 (22%)	
Nephr/heminephr/PU	9 (8%)	7 (10%)	0 (0%)	0 (0%)	1 (5%)	1 (11%)	
Other	3 (3%)	2 <sup>***</sup> (3%)	0 (0%)	0 (0%)	0 (0%)	1 <sup>***</sup> (11%)	
VUR, vesicoureteral reflux; postop obst, postoperative obstruction; reop, reoperation. Operations later in life: nephr, nephrectomy; heminephr, heminephrectomy; PU, pyeloplasty. Percentages in (parentheses) refer to total, percentages in [square brackets] refer to percentage of females and males, and percentages in <i>italic</i> refer to each flow curve shape group. <sup>*</sup> Colposuspension. <sup>**</sup> Rudimentary uterine horn. <sup>***</sup> Otis urethrotomy.							

Hutch (3), tunnel advancements (4), Williams (1), and extra-vesical operation (1).

Forty-three hospital staff members were selected as age-matched controls (Table 2) and went through exactly the same study protocol as the former VUR patients.

All patients had clean urine. Free flowmetry was performed with the use of a flowmeter with a spinning disc transducer (Dantec<sup>®</sup>, Dantec Electronics Ltd, Denmark) upon strong need to void. If necessary, up to two glasses of water were given to facilitate voiding. Patients and controls voided in their normal position. Residual urine was assessed by ultrasound by a urotherapist within 5 min after voiding, and was calculated with the use of the following bladder dimensions: [anterioposterior diameter (transverse image) × width (transverse image) × maximal sagittal diameter]/0.52. When more than 50 ml residual urine was measured or an abnormal urine flow curve was identified, the tests were repeated (48 patients).

The following test values were recorded: voided volume, maximum flow rate, average flow rates, and residual urine. Bladder capacity (BC) was calculated as a sum of voided volume and residual urine. Unmarked urine flow curve shapes were analyzed by two independent experienced urologists (T.L.-V., J.K.) who did not know patient histories. Curve shapes were classified by using the following criteria [13,14]: (1) “Normal”: a continuous hill-shaped flow curve, where maximum flow rate reaches a value between the 5th and 95th percentile in Liverpool nomograms. A small quantity of drops is allowed after the main stream. (2) “Tower”: a high flow curve whose height is double its width on a 50 ml/min scale and the maximum flow rate is more than the 90th percentile in the Liverpool nomogram. (3) “Weak” (plateau-shaped curves included): an elongated curve with a low maximum flow rate that is less than the 5th percentile in Liverpool nomograms, which is reached in the initial part of

the flow. (4) “Interrupted”: a repeatedly interrupted flow curve. (5) “Big bladder”: any continuous flow curve for which the BC is over 800 ml. In 35 cases of disagreement, the curves were reevaluated to achieve a mutual understanding. The patients were asked to answer questions (questionnaire and interview) on urinary symptoms concerning incontinence, urgency, and earlier UTIs.

Statistical analyses were performed with Microsoft Excel software (Microsoft Corp, Redmond, WA) using the Student *t* and chi-square tests with the Yate correction. *p* values less than 0.05 were denoted as significant, and *p* values between 0.05 and 0.1 as marginally significant.

### 3. Results

Results of classification of urine flow curves are shown in Tables 2 and 3. In females a normal flow curve shape was seen significantly more often (*p* = 0.0001) in controls (97%) than in patients with earlier VUR (63%). A weak, interrupted, and tower-shaped urine flow curve was seen in 14 (13%), 9 (8%), and 8 (7%) patients, respectively, but in none of the controls. In males a weak curve shape was registered in 7 patients (64%) and in 1 (17%) control (*p* = 0.2). Other males had normal flow curves.

Voided volumes, maximum and average flow rates, and residuals for each flow curve shape group are presented in Table 3. There were no significant differences in mean values for voided volumes between female (*p* = 0.5) and male (*p* = 0.5) patients and their controls. After exclusion of the big bladder group, there was little variation in voided volumes

**Table 3 – Free urine flow curve shapes with mean values (range of values in parentheses) for voided volumes, maximum and average flow rates, and residual urine volumes in female and male patients and their controls**

Flow curve shape			Voided volume (ml)		Maximum flow rate (ml/min)		Average flow rate (ml/min)		Residual (ml)	
	n	%	Mean	Range	Mean	Range	Mean	Range	Mean	Range
<b>Females</b>										
VUR patients										
Normal	69	63	373	136–749	30	14–51	16	2–35	10	0–101
Big bladder	9	8	913	786–1133	42	28–49	20	14–27	13	0–42
Tower	8	7	384	154–550	55	33–73	30	18–73	14	0–61
Weak	14	13	381	157–700	16	10–26	8	5–12	37	0–136
Interrupted	9	8	381	87–673	21	9–40	7	3–16	59	0–116
Total	109	100	420	87–1133	30	9–73	16	2–42	18	0–136
Controls										
Normal	36	97	380	128–780	34	15–59	18	6–37	12	0–128
Big bladder	1	3	813	813–813	47	47–47	24	24–24	0	0–0
Total	37	100	392	128–813	35	15–59	18	6–37	12	0–128
<b>Males</b>										
VUR patients										
Normal	4	36	272	201–360	21	20–25	12	11–15	8	0–23
Weak	7	64	567	400–702	19	14–26	11	7–14	37	0–136
Total	11	100	460	201–702	20	14–26	12	7–15	24	0–82
Controls										
Normal	5	83	369	185–680	23	16–28	15	11–18	1	0–3
Weak	1	17	510	510–510	17	17–17	11	11–11	2	2–2
Total	6	100	393	185–680	22	16–28	14	11–18	1	0–3

VUR, vesicoureteral reflux.

between the different flow groups, except for the significant difference ( $p = 0.0008$ ) in mean values between the normal and weak flow group in males.

Variation in maximum flow rates in females with earlier VUR was wide, the highest maximum flow rates (73 ml/s) being measured in the tower-shaped flow group and the lowest (9 ml/s) in the weak flow group, as expected. Although variation among female patients was similar to that in controls (15–59 ml/s), the mean maximum flow rate was significantly lower ( $p = 0.04$ ) in the patients. Among male patients maximum flow rate ranges and mean values ( $p = 0.3$ ) did not vary significantly from those in the controls.

The largest residuals were seen mainly in the interrupted (mean, 59 ml) and the weak (mean, 37 ml) flow groups in females. In the other flow groups the residuals were, on average, close to normal. Residuals equal to or over 100 ml were detected in only five female patients and in one female control. Two of them were seen in the interrupted, two in the weak, and one in the normal flow groups. There was no residual equal to or more than 100 ml in the male patient or control groups.

The distribution of operated female and male patients within the flow curve shape groups is shown in Table 2. The flow curve shape was markedly affected by treatment modality. A normal

flow curve shape was seen in only 20 of 44 operated patients (45%), whereas the percentage was 70 among the nonoperated patients and 95 in the controls. Forty-five per cent of the operated patients but only 13% of nonoperated patients had an interrupted or weak flow. The operations on subjects with a weak or interrupted flow curve shape had involved both ureters in 8 and 5 patients, respectively. Also, 2 patients with big bladder and 8 patients with normal flow had undergone a bilateral procedure. A reoperation was needed in 2, 3, and 2 patients with normal, weak, and interrupted flows, respectively.

Table 4 presents the symptoms of urgency incontinence and stress incontinence in the female patients and their controls classified according to their urine flow curve shapes. Neither the male patients nor the male controls reported these symptoms. Urgency incontinence was twice as common among the VUR patients compared with the controls ( $p = 0.5$ ). Urgency incontinence was detected predominantly (50%) in the tower-shaped flow group, being most uncommon in the weak flow group (7%). None of the controls and 6% of the patients had experienced urgency incontinence daily. Stress incontinence was experienced significantly ( $p = 0.05$ ) more often by patients (35%) than by controls (16%). As many as half of the patients in the



**Table 4 – Urgency incontinence, stress incontinence, and vaginal deliveries in flow groups in female patients and their controls**

	Flow curve shapes											
	Total		Normal		Big bladder		Tower		Weak		Interrupted	
	n	%	n	%	n	%	n	%	n	%	n	%
<b>Urgency incontinence</b>												
Patients												
Daily	7	6	5	7	0	0	1	13	0	0	1	11
Less frequently	15	14	8	12	1	11	3	37	1	7	2	22
Total urgency incontinence	22	20	13	19	1	11	4	50	1	7	3	33
No urgency incontinence	87	80	56	81	8	89	4	50	13	93	6	67
Total	109	100	69	100	9	100	8	100	14	100	9	100
Controls												
Daily	0	0	0	0	0	0	0	0	0	0	0	0
Less frequently	4	11	4	11	0	0	0	0	0	0	0	0
Total urgency incontinence	4	11	4	11	0	0	0	0	0	0	0	0
No urgency incontinence	33	89	32	89	1	100	0	0	0	0	0	0
Total	37	100	36	100	1	100	0	0	0	0	0	0
<b>Stress incontinence</b>												
Patients												
Daily	5	5	3	4	1	11	0	0	0	0	1	11
Less frequently	33	30	21	31	2	22	4	50	3	21	3	33
Total stress incontinence	38	35	24	35	3	33	4	50	3	21	4	44
No stress incontinence	71	65	45	65	6	67	4	50	11	79	5	56
Total	109	100	69	100	9	100	8	100	14	100	9	100
Controls												
Daily	1	3	1	3	0	0	0	0	0	0	0	0
Less frequently	5	14	5	14	0	0	0	0	0	0	0	0
Total stress incontinence	6	16	6	17	0	0	0	0	0	0	0	0
No stress incontinence	31	84	30	83	1	100	0	0	0	0	0	0
Total	37	100	36	100	1	100	0	0	0	0	0	0
<b>Vaginal deliveries</b>												
Patients	150	1.4	98	1.4	21	2.3	6	0.8	16	1.1	9	1.0
Controls	35	0.9	35	1.0	0	0	0	0	0	0	0	0

n = number; nd = number of vaginal deliveries; d/p = number of vaginal deliveries per person.

tower flow curve shape subgroup and almost half of the interrupted flow group presented with stress incontinence. The amount of daily stress incontinence was slightly more severe among the patients compared with the controls. The frequency of vaginal deliveries was higher in the patients than in the controls (1.4 per person and 0.9 per person, respectively). Urgency was reported slightly more

often ( $p = 0.6$ ) by female patients (31%) than by controls (24%). None of the controls had suffered from daily urgency, whereas it was a complaint of 14 (12%) patients.

Adulthood UTIs (Table 5) were reported significantly more often ( $p = 0.04$ ) by female patients (76%) than by female controls (57%). In 28 (25%) patients, but in no controls, UTIs were present even more

**Table 5 – Frequency of UTI in flow groups in female patients and their controls**

UTIs	Normal	%	Big bladder	%	Tower	%	Weak	%	Interrupted	%	Total	%	Controls	%
>1/year	17	25	1	11	1	12.5	5	36	4	45	28	25	0	0
Frequently	11	16	2	22	0	0	0	0	1	11	14	13	1	3
Few	30	43	3	33	1	12.5	4	28	3	33	41	38	20	54
UTI total	58	84	6	67	2	25	9	64	8	89	83	76	21	57
No UTI	11	16	3	33	6	75	5	36	1	11	26	24	16	43
Total	69	100	9	100	8	100	14	100	9	100	109	100	37	100

UTI, urinary tract infection.

>1/year means more than one infection yearly, few means 1–5 infections in adulthood, and frequently means the frequency between these two values.



often than once in a year. A high frequency of more than one infection per year was reported mainly by subjects in the interrupted flow group (45%) and the weak flow group (36%). Also 25% of patients with a normal urine flow curve shape suffered from UTIs more than once a year. None of the male patients or male controls had presented with adulthood UTI.

#### 4. Discussion

Our study showed an abnormal urine flow curve shape in 40% of the patients with VUR in their childhood, whereas two subjects in the control group had abnormal urine flow curve shapes (Tables 2 and 3). This finding is highly significant ( $p = 0.00005$ ). To our knowledge, this result is now reported for the first time among adults, although abnormal voiding patterns including interrupted voids, frequent small voids, and small bladder capacity have been reported in half of nonoperated infants with VUR [9,10].

A weak urine flow was seen in 18% and an interrupted curve shape in 8% of the participants with earlier VUR. These curve shapes are often associated with a weak detrusor or bladder outlet obstruction [15]. Anatomical obstruction in the urethra is unlikely because repeated voiding cystograms did not reveal any cases of urethral stricture in our patients. Abnormal urine flow findings were mainly recorded in those subjects who had had an operation for VUR in their childhood. Less than half (45%) of the operated patients voided normally. Two thirds of subjects with an interrupted or weak urine flow curve shape had undergone a reimplantation of the ureters, 13 of them had had a reimplantation for both ureters, and 6 of them needed a reoperation. Fung and associates [16] suggested neural damage of the detrusor from reimplantation of the ureters, especially in bilateral extravesical techniques. All except one of our operated patients had had an intravesical reimplantation of the ureter(s). Seventeen of the 21 operated patients with weak or interrupted urine flow curve shape had been operated on with techniques such as “submucous tunnel,” Politano-Leadbetter, and Hutch to divide the detrusor, which may in theory hamper bladder function. Indications for operational therapy varied during the 50s and 60s, but usually the most severe cases were operated on.

Another explanation for these abnormal voiding patterns is disturbed detrusor function and maturation during childhood, as proposed by Sillén and colleagues [17]. Because dyscoordination in voiding has been reported in 25–68% of children with VUR [6,7,17–19], an interrupted urine flow curve shape

may, in theory, be due to persisting childhood dysfunctional voiding. Forty percent of our patients with an interrupted or a weak flow curve shape had had dilating bilateral VUR during childhood. Although this percentage is double compared with patients with a normal flow curve shape, no conclusion that bladder dysfunction is associated especially with severe VUR can be drawn, because almost half of the patients with interrupted or weak flow curve shape had also undergone bilateral reimplantation of the ureters. Four of nine patients with an interrupted urine flow curve shape suffered from stress incontinence. Three of them had been operated on during childhood; one of them was nulliparous.

Bladder capacities in the study patients were generally similar to those in controls in other studies, except for 9 patients with more than 800 ml of BC [20]. Residuals in those with a weak or interrupted urine flow curve shape were higher than those in our controls, but differed little from other figures for control patients [20,21]. A high-capacity bladder may reflect a sensory defect of the bladder. Possibly high voiding pressures in infants with VUR also cause a sensory defect in the bladder, subsequently resulting in a lazy bladder. High voiding pressures have, however, previously been reported mainly in young males [22]. Weir and Jaques [23] found that 30% of patients with bladder capacities in excess of 800 ml were urodynamically normal. Also our patients with big bladders all had normal voiding frequencies and good voiding efficacies. Only three of them had been operated on for VUR.

A tower-shaped flow curve shape is often associated with a strong, overactive detrusor with or without a weak sphincter [24]. Patients with this flow curve shape had a low delivery rate, which speaks against low outflow resistance in these patients.

Half of the female patients suffered from urgency and urgency incontinence, indicating overactive detrusor. Although patients complained of these symptoms more than controls did, the differences were not significant. There might be an association between these irritative bladder symptoms and recurrent UTIs, which were also more common in the patients with earlier VUR than among the controls. The prevalence of these symptoms has not previously been reported in adults with earlier VUR, but detrusor overactivity is found in as many as 40–75% of children with VUR [8,25]. Stress incontinence was also presented more often ( $p = 0.05$ ) in the female study patients compared with the controls. Frequency of deliveries, however, was somewhat higher in the former group (Table 4). Male subjects in this study did not suffer from

incontinence or UTIs. Only two men had felt occasional urgency.

Seventy-six percent of females among our study patients had experienced UTI(s) during adulthood, which was significantly ( $p = 0.04$ ) higher than among controls (Table 5). The frequency of UTIs was also much higher in the subjects with VUR: One fourth of them had had UTIs more often than once every year. UTIs were most prevalent in females with interrupted or weak urine flow curve shape, the curve shapes which were also associated with the largest residuals. UTIs have previously been reported in 38% of surgically treated girls after 20-yr follow-up [26] and in 39% in a study of long-term follow-up, in which most of the patients were treated medically [5].

The number of subjects in some flow curve shape subgroups is relatively small, which makes comparison between different groups more difficult. A larger study group would have required patients from a much longer period of diagnosis, which would have resulted in greater variation in the age of the patients. We aimed, however, to explore voiding abnormalities in a cohort of patients at early middle age, before menopausal or prostatic problems. We could clarify the voiding pattern in two thirds of the patients, which is a fairly good result considering our exceptionally long follow-up time. Most of the subjects were females, which is consistent with the difference in prevalence between females and males suffering from VUR. Also women in this age group seem to be more motivated to participate in health studies.

## 5. Conclusions

Adult patients with childhood VUR have abnormal flow curve shapes and UTIs significantly more often than controls. Patients who had been operated on for reflux especially seemed to have an interrupted or weak uroflow. A great percentage of these patients also suffered from urgency and stress incontinence and annual UTIs.

## Conflicts of interest

The authors have nothing to disclose.

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### Editorial Comment on: Urine Flow Curve Shapes in Adults with Earlier Vesicoureteral Reflux

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The authors present an interesting study on the persistence of significant voiding and storage dysfunctions in a cohort of adult patients, who presented a history of vesicoureteral reflux (VUR) in childhood [1]. The study group included 120 patients, with a mean age of 41 yr, who had VUR diagnosed at a mean age of 4 yr. The refluxes were treated according to the standards adopted currently at that time, 35–40 yr ago. The study group was compared to an age-matched control group of 43 hospital staff members. All patients and controls had the same protocol, almost simple, consisting in an interview with micturition symptoms questionnaire, a single urine flowmetry, completed by ultrasound residual urine measurement and urine sample. If the residual urine was >50 ml, the monitoring was reiterated.

Abnormal curve shapes and urinary tract infections (UTIs) were more common in the study group of patients compared with the controls. The difference was more significant in the patients who underwent surgical correction of VUR in childhood; this subset of patients presented frequently weak or interrupted uroflow patterns, with a significant prevalence of urgency, stress incontinence, and recurrent UTIs.

During the last two decades, several studies have pointed out the strong correlation between VUR and bladder dysfunction in childhood [2,3]. We observe that poor information is still available on the long-term outcome of recurrent UTIs and voiding abnormalities in adult patients, who suffered from VUR in childhood. This paper, although simple in its methodology, offers an interesting answer, stressing that voiding dysfunctions may persist from childhood to adulthood and could be lifelong.

A weak point of the paper is the lack of information on the presence of voiding disturbances or bladder dysfunctional behaviour in the cohort of studied patients during childhood. Prospective longitudinal studies (possibly multicentre studies) should be strongly welcomed, to better understand the long-term outcome of bladder behaviour in patients with a history of VUR in infancy.

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# Urodynamical Findings on Women With Voiding Problems and Earlier Vesico-Ureteral Reflux

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**Aims:** Examine bladder function behind an abnormal urine flow curve pattern or lower urinary tract symptoms (LUTS) in women with earlier vesicoureteral reflux (VUR). **Methods:** Seventeen earlier female VUR patients with weak, fractionated or tower-shaped flow pattern, 10 patients with normal voiding and 2 patients with a big bladder were urodynamically studied. **Results:** A third of the patients had a large (>800 ml) cystometric bladder capacity. Sensitivity of the bladder was decreased especially in weak urine flow group. Half of these patients felt the “first sensation” when at least 40% of the bladder capacity was filled. Neither the earlier treatment modality nor grade of childhood VUR had an influence on the bladder sensitivity. Urinary tract infections were reported significantly more often ( $P = 0.028$ ) in patients with decreased bladder sensitivity than in the other patients. Overactive detrusor and decreased bladder compliance were uncommon findings. The detrusor pressure was good exceeding 15 cm H<sub>2</sub>O during the maximum flow rate in almost all patients. Abnormal sphincteric EMG activity during voiding was found in 70% of all patients and especially in fractionated flow group (89%). The EMG activity was seen twice as often in patients with earlier bilateral dilating VUR as in those who had suffered of non-dilating VUR ( $P = 0.005$ ). **Conclusions:** Despite of high frequency of symptoms in female patients with earlier VUR, detrusor overactivity was a rarity, but decreased sensitivity and large capacity of the bladder were found frequently. The patients with weak or fractionated urine flow seemed to suffer from an overactive urethral sphincter. *Neurourol. Urodynam.* 28:1015–1021, 2009. © 2009 Wiley-Liss, Inc.

**Key words:** bladder sensitivity; detrusor overactivity; sphincter activity; urodynamic study; VUR

## INTRODUCTION

Vesicoureteral reflux (VUR) during childhood has been associated with recurrent urinary tract infections (UTIs) and lower urinary tract dysfunction. VUR has been diagnosed in a third of the children with UTIs.<sup>1</sup> Risk of recurrent UTIs in adults with childhood VUR has been estimated to be about 40% no matter if VUR was treated surgically or medically.<sup>2</sup> Even two thirds of the children with VUR have been reported to suffer from detrusor overactivity or sphincter overactivity.<sup>3</sup> Some recent studies have also shown that half of the infants with VUR have an abnormal voiding pattern, including interrupted voidings, frequent small voids and small bladder capacity, meanwhile some other research groups claimed that the bladder capacity in VUR patients would be abnormally high.<sup>3,4</sup>

Our recent study showed that the urine flow curve pattern was significantly more often abnormal in adult patients with earlier VUR than in their age-matched controls. Abnormalities were found especially among patients who were operated on for VUR. Female patients of the study group suffered from stress and urgency incontinence twice more often than the controls. Also a quarter of the patients but none of the controls had had annual UTIs.<sup>5</sup>

Aim of our present study was to investigate urodynamically the bladder dysfunction causing these flow curve shape abnormalities and lower urinary tract symptoms (LUTS) in female patients.

## MATERIALS AND METHODS

The ethical review committee at Helsinki University Central Hospital (HUCS) approved this study. Out of 213

consecutive female patients who had been diagnosed for primary VUR (without outflow obstruction or neurological pathology) at HUCS between 1955 and 1965 150 women were reached and invited to participate with the first part of the study including a urine sample for bacteria, urine flowmetry, measurement of residual urine and filling up a questionnaire for LUTS. One hundred and fourteen patients completed this study (Fig. 1).

All patients had clean urine. Information of earlier UTIs was based on self-report. Results of urine flow pattern, residual urine and symptoms of these subjects, as well as the voiding symptoms questionnaire have been reported in our previous paper.<sup>5</sup> None of the patients were on anticholinergic medication. The patients were classified into five groups (Fig. 2) according to their spontaneous urine flow curve pattern using the criteria described previously:<sup>5</sup> (A) “normal”, (B) “tower”, (C) “weak” and (D) “fractionated”. Those with a large bladder capacity (>800 ml) formed a fifth group (E). All females with an abnormal flow pattern; 8, 15, and 10 patients from the groups B, C, and D were asked to participate with the second part of the study including a urodynamic study. Seventeen (51%) patients participated: two (25%) females from the tower group, six females (40%) from the weak group and nine (90%) females from the fractionated group. Additionally, 2 of 10

Conflicts of interest: none.

Rodney Appell led the review process.

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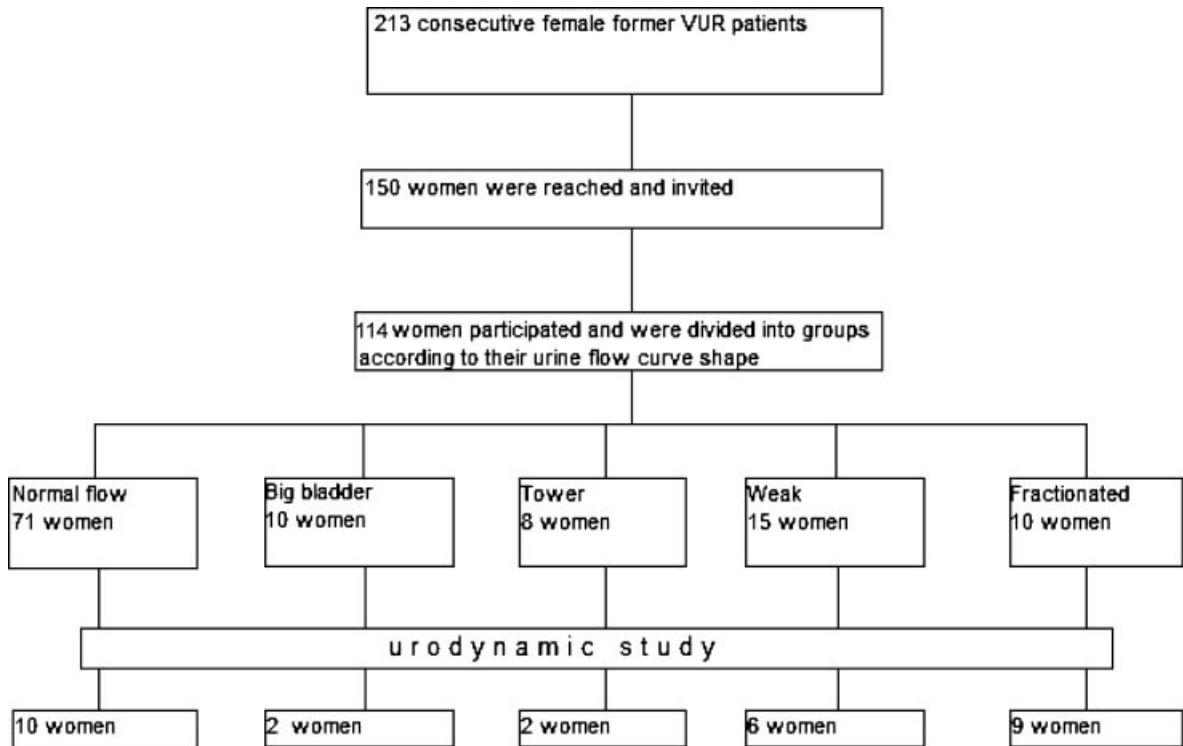


Fig. 1. Flow-chart of the study.

females (20%) who had a big bladder and 10 of 71 (14%) female patients who voided normally, but complained urinary symptoms, underwent a urodynamic study. Totally 29 urodynamic tests were performed. One patient could not void and her results we excluded from the pressure flow data.

Table I shows the characteristics of the final study groups (29 patients) including severity of VUR and the treatment given. There were three types of operations—all intravesical—which were used on our patients. Two of them “Hutch” and “submucous tunnel” included 2–4 cm long division of the detrusor, the third technique was Politano-Leadbetter. All subjects underwent a filling cystometry and a pressure-flow (pQ) study using a standardized urodynamic technique.<sup>6</sup> In cystometry (Dantec®, Menuet), the bladder was filled with water at room temperature with the infusion rate of 50 ml/min and voiding was performed in a sitting position. Bladder pressure was measured through a transurethrally inserted 2-lumen 6F cystometry catheter and a fluid filled open-end catheter was used to measure abdominal pressure. Surface electrodes were placed at the perineum for continuous pelvic floor electromyography (EMG).<sup>7</sup> UPP was measured using Brown-Wickman method with the infusion rate of 3 ml/min and withdrawal speed of 1.0 mm/sec.<sup>8</sup> All of the recordings were separately analyzed by two experienced urologists (TL-V and JV) without the person knowing patient histories. Urodynamic parameters were recorded and analyzed, see parameters and definitions in Table II.<sup>9–14,23</sup> The patients were asked to answer questions on urinary symptoms considering incontinence, urgency (see details in Ref.<sup>5</sup>) and earlier UTIs.

Thirty-seven hospital female staff members were selected as age matched controls to the cases for uroflowmetry, residual urine measurement and filling up the questionnaire. The mean age of the control group was 39 years (range 24–65 years).

Statistical analyses were carried out using Student's *t*-test and Fisher's Exact test on Microsoft Excel and StatistiXL software. *P*-values of at most 0.05 are denoted as significant, *P*-values between 0.05 and 0.1 as marginally significant.

## RESULTS

Classification of the urine flow curve shapes and voided volumes,  $Q_{\max}$  values as well as residuals for each flow pattern groups are presented in Table I. Table III shows the results of the symptom questionnaire. Seven of 10 patients with normal and 4 of 9 patients with fractionated urine flow pattern had suffered from LUTS. Other groups had had symptoms less often. In the control group there were 12 of 37 who had LUTS. Stress urinary incontinence was a complaint of 14 patients and of 6 controls. Of the 14 patients five suffered from it daily. Two of these five had a normal flow curve, two patients a fractionated curve shape and one had a big bladder. All but the one with a big bladder had been operated on; two by submucous tunnel, one by Politano-Leadbetter and one by Hutch.

There was no difference in the bladder sensitivity, number of patients who felt the FS when at least 40% of the bladder capacity was filled<sup>14</sup> between operated or conservatively treated patients or between patients with bilateral dilating reflux and non-dilating reflux (Table IV). One patient in the weak flow group was found to have an overactive detrusor. A decreased compliance of the detrusor was found in four patients, all belonging into the weak flow group.

Nine out of 30 patients had a large (>800 ml) cystometric bladder capacity. Large bladders were found evenly in all study groups. At least one patient in every group had large (>100 ml) residual urine in pressure flow study, except those

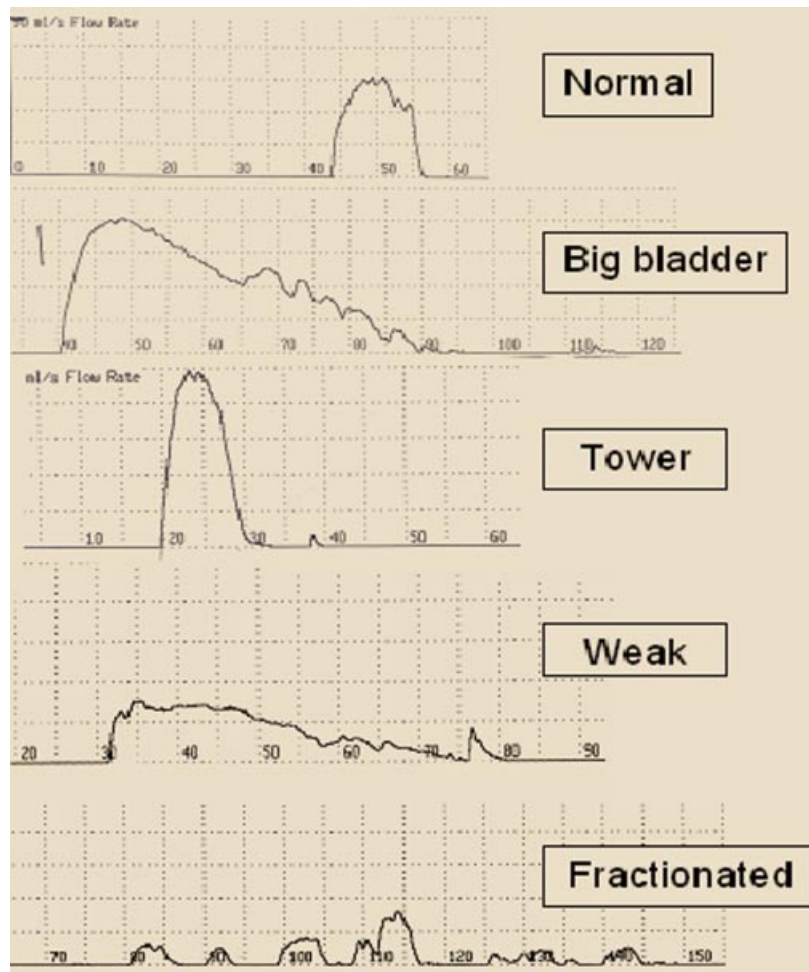


Fig. 2. The five patient groups according to the spontaneous urine flow curve patterns. For further details concerning the curve shapes see Ref.<sup>5</sup>

in the tower group. The average volume of the residual urine was largest (138 ml) among those with a fractionated urine flow.

Four out of 10 females who had presented with a normal urine flow curve shape had high ( $>35$  cm H<sub>2</sub>O)  $P_{det}Q_{max}$  value, but BOO was diagnosed only in one patient (Table V). Three of them had been operated on in their childhood. Activity in EMG was increased during voiding in seven patients of this group. The only patient with a repeatedly large volume ( $>800$  ml) bladder made a normal pressure voiding study including EMG activity. Both females of the "big bladder" group produced excellent  $Q_{max}$  values (45.4 and 65.0 ml/sec) with a relatively weak detrusor contraction (17 and 20 cm H<sub>2</sub>O) but different intravesical pressures at maximum flow rate ( $P_{ves}Q_{max}$ ) (32 and 140 cm H<sub>2</sub>O). Four females out of six with a weak urine flow curve shape voided with a high (42–77 cm H<sub>2</sub>O)  $P_{det}Q_{max}$  values, one of them had obstructed and two had equivocally obstructed voidings. These four females had abnormal sphincter activity during voiding; three of them had had surgical therapy for reflux in their childhood. The remaining two females of the weak flow group had relatively low  $P_{det}Q_{max}$  (16–21 cm H<sub>2</sub>O) with normal UPP max values and EMG activity during voiding.

Two of nine patients with fractionated voiding pattern had an equivocally obstructed voiding by the Griffith scale. These patients had the highest (95–101 cm H<sub>2</sub>O) maximum UPP

values of the group although EMG showed only slightly abnormal activity during voiding for one of them. All other patients of the group had abnormal EMG results. Value for BCI was high in three patients and low in one patient.

High  $P_{detmax}$  values ( $>38$  cm H<sub>2</sub>O) were measured in 11 of 12 patients who had been diagnosed with dilating bilateral reflux as a child. In those with non-dilating unilateral or bilateral reflux high pressure was seen in 5 of 10 patients ( $P=0.056$ ).

Patients with earlier dilating bilateral VUR had larger cystometric residuals (mean 139 ml) than those with bi or unilateral non-dilating reflux (mean 53 ml),  $P=0.04$ . In patients with higher VUR grade over 100 ml residuals were measured in six patients while only in one of the lower VUR grade patients,  $P=0.074$ . Patients with higher VUR grade had lower cystometric peak flow rates than patients with a lower VUR grade (20.9 ml/sec and 32.1 ml/sec,  $P=0.042$ ). Therefore, BCI was smaller in higher VUR grade patients, 144 versus 190,  $P=0.07$ .

## DISCUSSION

Although bladder function of the patients with VUR has been largely studied in pediatric population, there are no urodynamic studies on these patients in adulthood.<sup>3,4</sup> We earlier performed urine flow studies on a cohort of VUR-

TABLE I. Characteristics of the Study Groups

	Normal	Big bladder	Tower	Weak	Fract.	Total
Number of patients	10	2	2	6	9	29
Free flow data						
Max flow (ml/sec)	24** (16–30)	44 (41–46)	54** (48–60)	15** (10–23)	24** (9–41)	26 (9–60)
Voiding time (s)	34 (22–68)	48** (40–57)	10 (10)	76** (25–201)	107* (44–237)	67 (10–237)
Residual (ml)	24 (0–101)	14 (0–28)	4 (0–8)	43** (0–133)	59** (0–116)	37 (0–133)
Age						
Age at follow up, mean	39 (33–49)	38 (36–39)	35 (34–36)	39 (36–43)	39 (35–43)	38 (33–49)
Age at operation	4 (1–8)	6	No oper.	5 (4–7)	4 (2–8)	4 (1–8)
VUR characteristics						
Unilateral VUR	3	1	1	3	2	10
Bilateral VUR	7	1	1	3	7	19
Dilating VUR	7	1	0	4	7	19
Bilateral and dilat VUR	4	0	0	2	6	12
Double ureters	2	0	1	2	1	6
Treatment modality						
Conservatively treated	5	1	2	2	1	11
Operatively treated	5	1	0	4	8	18
Reimplantation, unilateral	2	1	0	2	2	7
Reimplantation, bilateral	3	0	0	2	6	11
Operation type						
“Hutch”	0	0	0	0	2	2
“Submucous tunnel”	4	1	0	1	5	11
“Politano-Leadbetter”	1	0	0	3	1	5
Re-operation	2	0	0	0	3	5
YV-plasty	1	No	No	No	1	2
Other bladder operations	1 colposusp	No	No	No	1 otis 30v	2

fract., fractionated; YV-plasty, bladder neck resection; colposusp., colposuspension; otis, otis' urethrotomy.

\*0.05 < *P* < 0.01 compared to the controls.

\*\**P* < 0.05 compared to the controls.

patients in their early middle ages, in age before menopausal or prostatic problems.<sup>5</sup> We found abnormal urine flow curve patterns in 33% and additionally 8% had a large bladder, the maximum flow rate was low in 18%, abnormally high in 7% and flow was interrupted in 8% of the patients. We performed a urodynamic study on these patients in order to examine bladder function behind these voiding abnormalities. About half of the patients were willing to participate, which we consider a fairly good result, in an invasive study like this. We also studied two patients with a big bladder and ten patients with a normal urine flow pattern with LUTS. In spite of relatively good participation rate the number of patients in some groups was very small which may influence the results and conclusions.

Detrusor overactivity is a common finding in children with VUR, although the prevalence reported has varied between 40% and 75%.<sup>15–17</sup> However, in the present study only one patient had as an adult slightly overactive bladder, although a third of the females had suffered from urgency and eight of 29 females from urgency incontinence. Detrusor overactivity may still cause the symptoms in these patients although this study did not find signs of it. Compliance of the bladder was only slightly decreased in three patients with a weak peak flow, but these patients did not suffer from incontinence.

Almost half of the study patients had delayed FS. This phenomenon was noticed in every group except the tower group. Since only half of these 12 patients were operated on for VUR during childhood, probably the earlier treatment modality was not associated with impaired sensation. VUR grade seemed not to be related to poor sensation as only a third of these patients had a bilateral dilating reflux. Some linkage between a large capacity and poor sensation of the

bladder was found since 4 of 12 patients with delayed FS had the bladder capacity over 700 ml.

In cystometry, one third of the patients had a bladder capacity of more than 800 ml, while it usually is less than 600 ml.<sup>18,19</sup> There are several possible explanations for a weak or distended detrusor muscle as a late sequence of VUR. Sillén et al.<sup>20</sup> postulated that a high capacity, over distended bladder, which is often poorly emptying and has low voiding detrusor pressures, is a common finding in children with congenital high-grade reflux. Seven out of 10 of our adult patients who had a large bladder in the cystometry had had earlier a dilating VUR. The treatment modality for VUR, however, did not affect on bladder size in adulthood.

A weak flow rate or a fractionated flow is usually thought to be caused by a weak detrusor or by functional or structural BOO. Our earlier uroflowmetry showed that 90% of the patients with a fractionated urine flow pattern had undergone a reimplantation of the ureter(s) using a technique which included detrusor division around ureter(s). Also 13 of 23 patients with a weak urine flow had had such an operation.<sup>5</sup> Since Fung et al.<sup>21</sup> reported on possible neural damage of the detrusor from reimplantation especially from bilateral extra-vesical techniques, we expected to find a weak detrusor in many of our patients. The  $P_{det}Q_{max}$ , however, was more than 15 cm H<sub>2</sub>O<sup>22</sup> in all but two women. On the contrary, high  $P_{det}Q_{max}$  values (>40 cm H<sub>2</sub>O) suggesting BOO,<sup>23</sup> were found in four of six females with a weak flow rate and in a third of those with a fractionated flow.

Dyscoordinated bladder in children with VUR has been a common finding.<sup>20,24–27</sup> Abnormal sphincteric EMG activity during voiding was found in 70% of our patients. It was seen most frequently in fractionated flow group (89%). Abnormal

TABLE II. Urodynamic Parameters and their Definitions

Filling phase
First sensation (FS)
Abnormal if >40% of bladder capacity <sup>14</sup>
Overactive detrusor
Unstable contractions $\geq 15$ cm H <sub>2</sub> O seen during filling phase
Decreased compliance
Base line $P_{det} > 15$ cm H <sub>2</sub> O during filling phase <sup>10</sup>
Pressure-flow
$Q_{max}$ (maximum flow rate)
Normal if >15 ml/sec <sup>18</sup>
$P_{det}Q_{max}$ (detrusor pressure at maximum flow rate)
Normal if >15 cm H <sub>2</sub> O and <40 cm H <sub>2</sub> O <sup>11</sup>
Bladder outlet obstruction (BOO)
$Q_{max} > 15$ ml/sec and $P_{det}Q_{max} \geq 35$ cmH <sub>2</sub> O <sup>12</sup>
$P_{detmax} > 40$ cm H <sub>2</sub> O <sup>23</sup>
$Q_{max} < 15$ ml/sec and $P_{det}Q_{max} \geq 20$ cm H <sub>2</sub> O <sup>13</sup>
Bladder outlet obstruction index (BOOI)
$P_{det}Q_{max} - 2 \times Q_{max}$ <sup>9</sup>
Voiding obstructed if BOOI > 40
Voiding equivocal if BOOI 20–40
Voiding unobstructed if BOOI < 20
Bladder contractibility index (BCI)
$P_{det}Q_{max} + 5Q_{max}$ <sup>9</sup>
Ability to contract strong if BCI > 150
Ability to contract normal if BCI 100–150
Ability to contract weak if BCI < 100
Bladder capacity
Voided volume + residual urine (measured by emptying the bladder through a catheter after micturition)
Electromyocardiography of the sphincter (EMG)
Analyzed visually <sup>6</sup>
Urethral pressure profile (UPP)
Analyzed visually <sup>7</sup>

EMG activity during voiding seemed to be influenced by the grade of VUR. All 12 patients with bilateral dilating reflux had this activity, but only 5 of 10 patients with non-dilatating bi or unilateral reflux had it ( $P = 0.005$ ). As Pauwels et al.,<sup>22</sup> did not find any increase in surface EMG recordings during pQ study even when straining in healthy middle-aged women, our

TABLE IV. Abnormal Findings During the Filling Phase

Free flow pattern	Big bladder				Fractionated	Total
	Normal	Tower	Weak			
Number of patients	10	2	2	6	9	29
FS > 40% of BC	5	1	0	3	3	12
Overactive detrusor	0	0	0	1	0	1
Decreased compliance	0	0	0	3	0	3
$P_{det} \geq 15$ cm H <sub>2</sub> O						

findings are probably caused by true dysfunction of the sphincter. Also a marginally significant difference ( $P = 0.074$ ) was detected in cystometric large residuals when comparing patients with earlier bilateral dilating reflux (residual over 100 ml in six patients) to those with earlier non-dilating bi or unilateral reflux (residual over 100 ml in one patient). Operation did not have effect on EMG activity nor on  $P_{detmax}$ . Overactive sphincter may be caused by over practised sphincter to prevent leakage from an overactive bladder in childhood. It is, however, hard to say if the voiding disturbance in adulthood is caused by primary bladder dysfunction, surgery or bilateral ureteral dilatation as such. We could not find other causes of poor coordination between detrusor and urethral sphincter such as areflexive, weak or overactive detrusor and involuntary or voluntary contraction of the external sphincter during voiding.

Almost half of our female patients were complaining stress incontinence, urgency incontinence or urgency. As symptoms are not caused by overactive detrusor, they may be caused by recurrent UTIs. Forty-five percent of the females with symptoms had recurrent UTIs which is in accordance with the high UTI frequency in adult females with childhood VUR reported earlier.<sup>2,5</sup> Frequency of the UTIs, however, was based on self-report and thus is not completely reliable. In this study especially females with the fractionated urine flow pattern have had UTIs, half of them more often than annually. Most of our patients with normal voiding also suffered from UTIs, but this group of women participated with the study because they

TABLE III. Symptoms in Patients and Controls

Free flow pattern	Patients						Controls
	Normal	Big bladder	Tower	Weak	Fract.	Total	Total
Number of patients	10	2	2	6	9	29	37
Urgency							
Daily	5	0	0	0	1	6	0
Less frequently	2	0	1	0	2	5	9
Urgency incontinence							
Daily	3	0	0	0	1	4	0
Less frequently	2	0	1	0	1	4	4
Stress incontinence							
Daily	2	1*	0	0	2	5 (1of*)	1*
Less frequently	3 (2of*)	1*	1	2 (1of*)	2 (1of*)	9 (4of*)	5 (3 of*)
Deliveries/mother (sections excluded)	1.3	2.5	0.5	1.5	0.8	1.2	0.9
Uniparous or multiparous	7	2	1	4	5	19	17
Nulliparous	2	0	1	1	4	8	20
Mothers with sections only	1	0	0	1	0	2	3
UTIs							
>1/year	5	0	1	1	4	11	0
Frequently	1	1	0	0	1	3	1
1–5 in adult life	3	0	0	3	3	9	20
None	1	1	1	2	1	6	16

Fract., fractionated.

\*after delivery.



TABLE V. Pressure Flow: UPP, EMG, Data

Free flow pattern	Normal	Big bladder	Tower	Weak	Fractionated	Total
Number of patients	10	1	2	6	9	28
$Q_{\max}$						
Max flow, mean (ml/sec)	25	21	55	20	22	29
$Q_{\max} \leq 15$ ml/sec	2	0	0	2	1	5
$Q_{\max} < 12$ ml/sec	1	0	0	1	1	3
$P_{\det Q_{\max}}$						
$P_{\det Q_{\max}}$ , mean (cm H <sub>2</sub> O)	27	25	19	48	33	30
$P_{\det Q_{\max}} < 15$ cm H <sub>2</sub> O	1	0	0	0	1	2
$P_{\det Q_{\max}} \geq 35$ cm H <sub>2</sub> O	4	0	0	4	3	11
$P_{\det Q_{\max}} > 40$ cm H <sub>2</sub> O	1	0	0	4	3	8
BOO						
BOO $\leq 15$ ml/sec and $\geq 35$ cm H <sub>2</sub> O	0	0	0	1	1	2
BOO $< 15$ ml/sec and $\geq 20$ cm H <sub>2</sub> O	1	0	0	1	1	3
$P_{\det Q_{\max}} > 40$ cm H <sub>2</sub> O	1	0	0	4	3	8
Bladder contractility						
BCI, mean	151	128	295	145	144	173
BCI $< 100$ (weak)	2	0	0	1	1	4
BCI $> 150$ (strong)	4	0	2	3	3	12
$P_{\det \max}$						
$P_{\det \max}$ , mean (cm H <sub>2</sub> O)	41	46	21	60	47	43
$P_{\det \max} \geq 38$ cm H <sub>2</sub> O	8	1	0	4	7	20
$P_{\det \max} \geq 40$ cm H <sub>2</sub> O	6	1	0	4	6	17
EMG						
EMG activity during voiding	7	0	1	4	8	20
UPP						
UPP max $< 40$	2 (of 9 pts)	1	0	1 (of 5 pts)	2	6 of 26
UPP max $> 80$	1 of 9	1	1	0	3	6 of 26

had symptoms. Frequency of UTIs in adulthood was not significantly associated either with bilaterality or grade of earlier VUR. Although after spontaneous voiding, mean urine residual volume of the females with a weak or fractionated voiding pattern exceeded that of our controls ( $P = 0.0037$ ) it did not differ much from residual volumes of healthy females reported by other authors<sup>18</sup> and thus does not fully explain the high frequency of UTIs. Those who had had a reimplantation of the ureter(s) in their childhood suffered especially from UTIs. In our study 14 out of 18 operated patients had had UTIs during adulthood; half of them more than once a year. Cystometric residuals higher than 100 ml were recorded marginally more often in the operated patients than in their non-operated peers. Recurrent UTIs seemed also to be associated with increased EMG activity during voiding. The female patients suffering from frequent or annual UTIs had pathological EMG activity significantly more often ( $P = 0.0038$ ) than the other study patients. Barroso et al.<sup>28</sup> found that vesicourethral dysfunction was present in 87% of scholar children with UTIs. This suggests that a possible overactive urethra and inclination to get UTIs in childhood may persist in some patients in adulthood. Urinary tract infections were also highly associated with decreased sensation of bladder ( $P = 0.028$ ). All patients with delayed FS had suffered from UTIs during their adult life. One explanation could be that an overactive bladder gives frequently sensation of urgency during an inhibited detrusor contraction which a child may learn to neglect what could result infrequent voiding habit resulting a large bladder capacity and UTIs.<sup>29</sup>

### CONCLUSIONS

Despite of high frequency of urgency and urgency incontinence in patients with earlier VUR, detrusor overactivity was

an infrequent finding. Cystometric bladder volume was large in one third of the patients. First sensation of the bladder fullness was delayed in a third of the participants, which was highly associated with UTIs in adulthood. Recurrent UTIs were also associated with pathological EMG activity during voiding and the high grade of earlier VUR. A weak or fractionated urine flow pattern in these patients was caused by overactive urethral sphincter rather than by a weak detrusor. Patients with earlier re-implantation did not have more voiding disturbances than conservatively treated patients, but suffered more often from recurrent UTIs. Patients with earlier bilateral dilating VUR, who were mostly operated on, had on average higher  $P_{\det \max}$ , more often EMG activity during voiding and larger post-void residuals than patients with non-dilating reflux.

### ACKNOWLEDGMENTS

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# The association of adult kidney size with childhood vesicoureteral reflux

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## Abstract

**Background** We used ultrasound to measure kidney volumes in adults with a history of childhood vesicoureteral reflux (VUR) and assessed whether total renal volume, small kidney size or the thickness of the upper pole correlated with renal function or hypertension.

**Methods** The kidneys of 123 adults were studied by ultrasound, calculating their volumes using an ellipsoid formula normalised to body surface area ( $\text{Vol}_N$ ). The thickness of the upper pole parenchyma and the number of small kidneys (<80% of normal volume) were recorded. Blood pressure measurements and laboratory tests were also performed.

**Results** Kidneys with a history of VUR were 12% smaller than those without known VUR ( $p<0.05$ ), and those with prior dilating VUR were 16% smaller than those with non-dilating VUR ( $p<0.05$ ). There was a moderate correlation ( $r=0.42$ ,  $p<0.05$ ) between total  $\text{Vol}_N$  and GFR values in the total patient series. Thirteen percent of the patients had a moderate decrease in kidney function. The occurrence of hypertension and

proteinuria was not affected by either kidney size or a thin upper pole.

**Conclusions** Total  $\text{Vol}_N$  in ultrasound in early adulthood could probably predict possible renal deterioration in later life. The occurrence of one small kidney was a common finding and seemed not to affect the prevalence of proteinuria or hypertension.

**Keywords** Kidney volume · Kidney function · VUR · Ultrasound · Parenchymal thickness · Hypertension · Proteinuria · Upper pole thickness

## Introduction

Kidney growth in patients with vesicoureteral reflux (VUR) is usually measured by ultrasound. Although scars are not seen on ultrasound as well as on a dimercaptosuccinic acid (DMSA) renal scan, ultrasound has many advantages. It is non-invasive, safe, easily available and inexpensive. There is evidence that decreased kidney function and hypertension in patients with VUR are associated with renal scars [1–3]. Also, a relationship between total kidney volume measured by ultrasound and lowered kidney function has been reported by Kim et al. [4]. While kidneys with dilating VUR (grades 3–5) are monitored with periodic ultrasound scans throughout growth, no guidelines exist for monitoring non-dilating VUR (grades 1–2) [5]. The aim of the present work was to explore whether total normalised renal volume, small kidney size or the thickness of the upper pole, as measured by ultrasound, correlated with renal function or hypertension in adult patients with a history of childhood VUR. A further intention was to study the implications of the severity of earlier reflux and age at diagnosis on the renal outcome.

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## Subjects and methods

### Patients

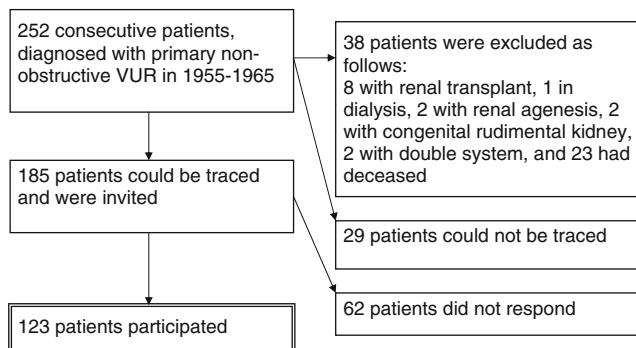
Out of 252 consecutive patients diagnosed with primary non-obstructive VUR (without ureteral or bladder outflow obstruction or neurological pathology) after febrile urinary tract infections in childhood, 185 were contacted in adulthood. One hundred and twenty-three (66%, 14 men) responded and were accepted for the study (Fig. 1). The baseline characteristics of these patients are listed in Table 1.

### Protocol

All the patients had been treated at the Children's Hospital in Helsinki between 1955 and 1965. Now, in adulthood, they underwent laboratory tests, renal ultrasound, measurements of weight, height and blood pressure (BP) and finally an interview concerned with general health, medication and surgery. A more detailed description of the group is given by Lahdes-Vasama et al. [1].

### Baseline data: examinations and treatments in childhood

Vesicoureteral reflux was graded as “dilating” (grades 3–5) or “non-dilating” (grades 1–2), according to the childhood cystogram reports. There were 45 patients with unilateral or bilateral non-dilating VUR, the mean ages at diagnosis being 4.7 and 4.1 years respectively. The indication for a cystogram had been at least one febrile urinary tract infection, but usually there had been recurrent infections. The urogram reports for all the patients were also reviewed to exclude obstructive conditions. There were no cases of neurogenic bladder or urethral valve complications in the group. Five of the 45 non-dilating VUR patients and 35 of the 78 dilating cases were operated on ( $p=0.0001$ ). The indications for surgery varied so that it was usually the most severe cases that were operated on. A re-operation was needed for 10 patients owing to ureteral obstruction or severe residual reflux.



**Fig. 1** Flow chart of the study patients

**Table 1** Baseline data on the patients

	Women	Men
Number of patients (%)	109 (89)	14 (11)
Years (range)		
Age at diagnosis	4.5 (0.2–16)	2.9 (0.2–7)
Age at operation	5.4 (1–15)	4 (2–6)
Characteristics of VUR		
Right-sided VUR	20	1
Left-sided VUR	28	5
Bilateral VUR	61	8
Dilating VUR	68	10
Bilaterally dilating VUR	33	4
Double system <sup>a</sup>	18	1
Operative treatment		
Operation for VUR	40	3
Operation for bilateral VUR	23	2
Re-operation for VUR/obstruction	8	2
Nephrectomy/heminephrectomy <sup>a</sup>	3/4	0/0

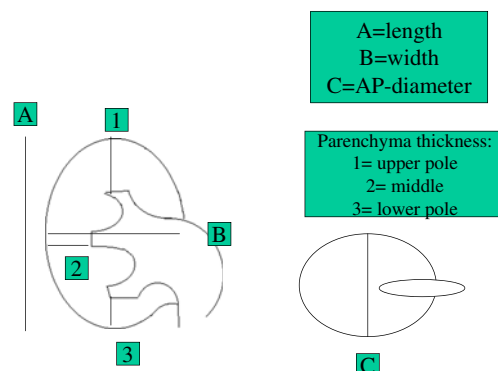
<sup>a</sup> Omitted from the data on kidney dimensions

VUR, vesicoureteral reflux

Conservative treatment consisted of follow-up with or without prophylactic antibiotic therapy (nitrofurantoin or sulfonamide) for a varying period of time. Persistent reflux in adulthood was found by cystogram in 8 patients (7%).

### Ultrasound data

Ultrasound was performed on all the adult patients, 69 with an ATL 5000 device (Advanced Technology Laboratory, 1998) using a convex C5-2 MHz probe, 42 with an ATL 3000 (1996) using a C7-4 MHz convex probe and P2-3 phased array probes and 12 with an Acuson 128XP/10M device (1993). Nine dimensions were measured twice for each kidney by an experienced radiologist (Fig. 2), and the mean values were recorded. The width and thickness were



**Fig. 2** Ultrasound measurements of the kidney

measured in a section perpendicular to the longitudinal axis of the kidney as assessed from the longitudinal image. Kidney volume was calculated using an ellipsoid formula: kidney length  $\times$  width  $\times$  AP diameter  $\times$  0.52 [6].

The effect of the patient's size was normalised by dividing the kidney volume by the body surface area (BSA) calculated by the Mosteller method [7]. The normal relative kidney volume was taken to be the mean volume of the right or left kidney in a group of patients without renal scars seen on ultrasound and without any previous ipsilateral vesicoureteral reflux. The normal value for the total relative kidney volume ( $\text{Vol}_{\text{TN}}$ ) was taken to be the mean total kidney volume in a group of patients without renal scarring seen on ultrasound. The mean relative volume on the left side was  $69 \text{ mL/m}^2$  and that on the right side  $65 \text{ mL/m}^2$ . The mean  $\text{Vol}_{\text{TN}}$  was  $135 \text{ mL/m}^2$ . A kidney was considered small if it was less than 80% of the mean relative volume. The maximum relative size of a “small kidney” was  $56 \text{ mL/m}^2$  on the left side,  $52 \text{ mL/m}^2$  on the right side and  $108 \text{ mL/m}^2$  on both sides. The normal upper pole parenchymal thickness was taken to be the mean diameter of the parenchyma on both sides in patients without any renal scars visible on ultrasound and without any previous ipsilateral VUR. The average thickness of the upper pole parenchyma of scarless kidneys without earlier VUR was 1.63 cm for the right side and 1.83 cm for the left side. The upper pole parenchyma was considered thin if it was less than 80% of the above-mentioned normal value. Twelve patients (1 male) with a unilateral double system and 2 with a bilateral double system were included in the study with the exception of the measurements of the length and width of their double kidney. Data on the resected kidneys were excluded from the kidney length, width and upper pole parenchyma thickness results, but not from those concerned with kidney volume.

## Outcomes

Overnight fasting blood and urine samples were obtained from each participant between 8 and 12 a.m. The serum samples were analysed for creatinine and the urine samples for creatinine, albumin and protein. To evaluate glomerular damage, total protein and albumin excretion values were measured in relation to creatinine excretion in the urine spot samples. Urine creatinine excretions were calculated and the reference values used were  $<3.0 \text{ mg/mmol}$  creatinine for albumin and  $<20 \text{ mg/mmol}$  creatinine for total protein [8]. GFR was calculated from the Modification of Diet in Renal Disease (MDRD) value for all patients:  $\text{GFR} = 175 \times (\text{serum creatinine concentration} / 88.4) - 1.154 \times (\text{age}) - 0.203 (\times 0.742 \text{ for women})$  [9]. Kidney function was regarded as normal or mildly reduced when the result was at least  $60 \text{ mL/min/1.73 m}^2$  and moderately or severely impaired

when the value was 30–59 and 15–29  $\text{mL/min/1.73 m}^2$  respectively. Those who scored less than  $15 \text{ mL/min/1.73 m}^2$  were regarded as suffering from terminal uraemia [10].

Blood pressure (BP) was measured from both arms after 15 min in a sitting position. The mean values of these two measurements were expressed as SD using the normal data of O'Brien et al. [11]. Readings higher than 2 SD for age and sex were recorded as hypertensive, together with 13 patients already receiving antihypertensive medication. Other examinations included urine flowmetry, measurement of residual urine and a questionnaire on lower urinary tract symptoms (LUTS). These results have been reported elsewhere [12].

## Statistical analyses

Fisher's exact test, the Mann–Whitney *U* test and multivariate logistic regression analysis as included in the Microsoft Excel, StatistiXL and SPSS software packages were used for the statistical analyses. *p* values below 0.05 were considered significant. Pearson's correlation coefficient was used to determine the degree of association, where  $r=0$ –0.19 was regarded as a very weak correlation, 0.2–0.39 as weak, 0.40–0.59 as moderate, 0.6–0.79 as strong and 0.8–1 as very strong [13].

## Ethical aspects

The protocol was approved by the ethics review committee of Helsinki University Central Hospital.

## Results

A unilateral small kidney ( $<80\%$  of “normal volume”) was seen frequently (in 47% of the patients, Table 2), and

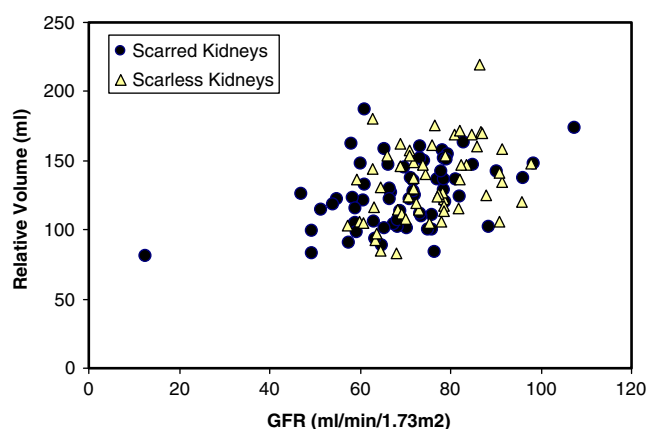
**Table 2** Effect of kidney size on glomerular filtration rate (GFR), proteinuria/albuminuria and hypertension. A small kidney is defined as being less than 80% of the size of a normal kidney

Kidneys	All	1 small	2 small	Normal size
<i>n</i> (%)	119 <sup>a</sup>	56 (47%)	8 (7%)	55 (46%)
GFR ( $\text{mL/min/1.73 m}^2$ )	72.6	69.2	64.1	77.2
GFR $<60 \text{ mL/min/1.73 m}^2$	17 (14)	12 (21)	2 (25)	3 (5)
<i>n</i> (%)				
Proteinuria and/or albuminuria	19 (16)	8 (14)	2 (25)	9 (16)
<i>n</i> (%)				
Thin upper pole bilaterally	5 (4)	2 (4)	1 (13)	2 (4)
<i>n</i> (%)				
Hypertension	39 (33)	15 (27)	4 (50)	20 (36)

<sup>a</sup> Three patients who had undergone nephrectomies and 1 patient with height and weight data missing were excluded

kidneys with a history of VUR were 12% smaller than those without known VUR—the normalised mean average volumes ( $\text{Vol}_N$ ) being  $64 \text{ mL/m}^2$  and  $73 \text{ mL/m}^2$  respectively ( $p=0.003$ ). The severity of childhood VUR affected renal size in that the kidneys with a history of dilating VUR (grades 3–5,  $\text{Vol}_N$   $59 \text{ mL/m}^2$ ) were 16% smaller than those with non-dilating VUR (grades 1–2,  $\text{Vol}_N$   $70 \text{ mL/m}^2$ ),  $p=0.001$ .  $\text{Vol}_N$  with a history of dilating VUR was 18% smaller than in kidneys without any known VUR ( $p=0.0001$ ) and that in non-dilating VUR was 3% smaller ( $p = \text{ns}$ ). The mean  $\text{Vol}_{TN}$  in patients with earlier dilating VUR on either one side or both sides was  $126 \text{ mL/m}^2$  (range 81–187) and that in patients with earlier non-dilating VUR was  $136 \text{ mL/m}^2$  (range 89–219;  $p=0.08$ ).

When patients were divided into three groups depending on their normalised kidney volume (one small kidney, two small kidneys and two normal-sized kidneys; see Table 2), those with normal-sized kidneys had 10% higher GFR values than those with at least one small kidney ( $p=0.0001$ ), a statistical difference that was not affected by the inclusion of age at diagnosis, gender, body mass index (BMI) or ultrasound-detected kidney scarring in the regression analysis. The patients with one or two small kidney(s) with ( $p=0.0003$ ) or without ( $p=0.01$ ) renal scars seen on ultrasound had significantly reduced GFR relative to those with normal-sized kidneys without scarring. The GFR of patients with non-dilating VUR in childhood was on average  $74.9 \text{ mL/min/1.73 m}^2$  and that in the dilating group  $71.1 \text{ mL/min/1.73 m}^2$ ,  $p = \text{ns}$ . There were 4 patients (9%) in the non-dilating group with a GFR value below  $60 \text{ mL/min/1.73 m}^2$  and 13 (17%) in the dilating group ( $p = \text{ns}$ ). The correlation of kidney function (GFR) with normalised total kidney volume in the total set of patients was moderate ( $r=0.42$ ,  $p=10^{-6}$ ), as seen in Fig. 3.



**Fig. 3** Scatter diagram of the relation between the glomerular filtration rate (GFR) and the total normalised kidney volume in the total series of patients ( $r=0.42$ ,  $p=0.000001$ ), divided into the following groups: patients with unilateral or bilateral renal scars visible on ultrasound (circles,  $r=0.44$ ,  $p=0.0002$ ) and patients with no renal scars visible on ultrasound (triangles,  $r=0.36$ ,  $p=0.006$ )

Hypertension was seen in 50% of patients with two small kidneys, and in 27% and 36% of patients with one small kidney and two normal kidneys respectively. The differences between the groups were not significant. Proteinuria, also defined as albuminuria, was seen in 25% of patients with two small kidneys, 14% of those with one small kidney and 16% of those with two normal-sized kidneys,  $p = \text{ns}$  between all the groups. When the former VUR patients with at least one small kidney were compared with those with normal-sized kidneys, no statistically significant differences could be seen in the incidence of proteinuria, bilateral upper pole thinning or hypertension—results that were not altered by the inclusion of age at diagnosis, gender or BMI in the regression analysis. The OR seen in cases of proteinuria was nevertheless 3.1 ( $p=0.047$ ) in patients with a scarred kidney visible on at least one side on ultrasound and 2.3 ( $p=0.054$ ) in hypertensive patients with BMI over 30, compared with the abovementioned groups (Table 2).

Patients who had been diagnosed with VUR before the age of 2 years had smaller kidneys than those with a diagnosis reached after 2 years of age ( $\text{Vol}_{TN}$   $118 \text{ mL/m}^2$  vs  $133 \text{ mL/m}^2$ ;  $p=0.007$ ), but there were no differences between the groups in terms of average GFR values ( $71.6$  vs  $72.7 \text{ mL/min/1.73 m}^2$ ), hypertension (29% vs 34%) or proteinuria (14% vs 11%). A GFR less than  $60 \text{ mL/min/1.73 m}^2$  was found in 5 patients (18%) and 12 patients (13%) respectively,  $p = \text{ns}$ .

The upper pole parenchyma was on average slightly thicker in the right kidney (1.76 cm) than in the left kidney (1.70 cm;  $p = \text{ns}$ ), and 44 patients (38%) had a thin upper pole in at least one kidney. Kidneys with scarring visible on ultrasound had the upper pole parenchyma narrowed by 0.2 cm on the right side and by 0.3 cm on the left side ( $p=0.03$  and  $0.003$  respectively). Thirty-five percent of the patients with a thin upper pole had hypertension, whereas 32% of those with normal upper poles were hypertensive ( $p = \text{ns}$ ). Thirty-five percent of the hypertensive patients and 36% of the normotensive patients had a thin upper pole in at least one kidney ( $p = \text{ns}$ ).

## Discussion

The ultrasound findings presented here show that kidneys with a history of VUR were significantly smaller than those without any known VUR. Also, those with prior dilating VUR were smaller than those with non-dilating VUR. There was a moderate correlation between total  $\text{Vol}_N$  and the GFR values. Thirteen per cent of patients had a moderate decrease in kidney function. The occurrence of hypertension and proteinuria was not affected by kidney size or by the presence of a thin upper pole.

The participation rate was relatively good (66%), and although women were overrepresented, this was partly



caused by the natural distribution of VUR between the genders. VUR of grades 1–2 is often excluded from assessments of the effects of the disease, although both hypertension and chronic renal insufficiency have also been associated with the mildest forms of VUR [14]. Even though the probability of hypertension and the risk of chronic kidney disease both increase with age in patients with earlier VUR, only a few papers have been published that are concerned with these patients in their 40s [15, 16].

The present series included patients with all grades of VUR. The original mictocystography (MCG) pictures were not available for examination; thus, our classification was based on reports only. The number of patients with clinical findings such as hypertension or proteinuria was small, which may have influenced the results and conclusions.

As a non-invasive imaging technique, ultrasound is a frontline modality for screening kidney abnormalities. Other authors report 32–58% of patients with childhood VUR to have renal scars, but not all the scars are significant [1, 3, 17]. Although the sensitivity of ultrasound for visualising scars is poorer than that of DMSA [18], ultrasound is a valuable and easily repeatable tool for evaluating kidney size. The aim here was to use ultrasound to measure the size of kidneys affected previously by VUR to find out whether their volume has any correlation with kidney-related problems in these patients. All the ultrasound-detected kidney dimensions in our patients were smaller on average than those reported previously for healthy populations [19].

Sanusi et al. [20] reported that kidney volume determined on ultrasound (calculated using the same formula for an ellipsoid organ as in the present work) correlated with the GFR of patients with chronic kidney disease. We also normalised the kidney volume by dividing the actual volume by the patient's BSA and found that the normalised kidney volume correlated well with the GFR in healthy subjects [4, 21]. The Vol<sub>TN</sub> (135 mL/m<sup>2</sup>) of our patients without renal scars was on average 26% lower than that of the healthy female subjects reported by Rasmussen et al. in 1978 [22], which suggests that their kidney growth had been affected by the earlier VUR and pyelonephritis, even though no renal scars were seen on ultrasound.

A unilateral small kidney (<80% of “normal volume”) was a common finding in patients with renal scars, but those whose kidneys seemed to be scarless on ultrasound also frequently had a small kidney. One small kidney did not seem to be associated with abnormal kidney function, but patients with bilateral small kidneys more often had lowered GFR values. The correlation observed here between Vol<sub>TN</sub> and GFR is in line with the finding of Sanusi et al. [20] that kidney volume determined on ultrasound correlated weakly, but positively with the GFR of patients with chronic kidney disease. Kim et al. [4] found closer correlation between GFR

and BSA-normalised volumes measured by 2D, and especially 3D, ultrasound ( $r=0.696$  and  $0.809$  respectively) in patients with chronic renal disease. Renal scarring may take a variety of forms, however, and VUR can lead to growth failure even without scarring, as described by Smellie et al. [23]. We found small kidneys in 20% of the patients with earlier non-dilating VUR, compared with 27% of the patients with earlier dilating VUR. It is possible that small scars are missed on ultrasound, but it is in any case unlikely that small local scars would affect kidney size. Thus, small kidneys without scars seen on ultrasound are cases of intra-renal scars. There are no earlier reports on “small kidney size” in patients with earlier VUR.

We wanted to test a clinical hypothesis that thinned upper pole parenchyma might be associated with the development of renin-mediated hypertension. Levy et al. [24] studied patients with renal duplication and upper pole ureterocele, and hypothesised that preservation of the functional upper pole moiety may increase the incidence of hypertension. Although patients who had an upper pole salvage operation had hypertension twice as often as those whose upper pole was removed, they could not assign any statistical significance to this finding. In our series, a thin upper pole was found in 39% of the hypertensive patients and 36% of the normotensive patients.

The patients who had been diagnosed with VUR before the age of 2 years had a significantly smaller Vol<sub>TN</sub> than the others, but no difference in average GFR values was seen between the age groups. Patients with GFR values less than 60 mL/min/1.73 m<sup>2</sup> were nevertheless detected 5% more often in the group of younger patients. This finding, albeit non-significant, differs from the observations of Silva et al. [2], who studied children with severe VUR and concluded that age over 24 months at diagnosis is more often associated with chronic kidney disease, defined as GFR <75 mL/min/1.73 m<sup>2</sup>.

Since low-grade VUR (grades 1–2) in childhood is associated with normal renal growth and function, it is not usually treated [5] or even followed up. The present patients with previous non-dilating VUR ( $n=45$ ) ended up with a normal kidney size on average and fewer of them had renal scars than those who had had severe VUR. Four of the patients with non-dilating VUR had moderately lowered GFR values (<60 mL/min)—2 of them had renal scars and the other 2 a small Vol<sub>TN</sub>. More patients with non-dilating VUR also presented with proteinuria and hypertension than those with dilating VUR. This suggests that the decision as to whether or not to place VUR patients under observation cannot be based purely on the severity of VUR.

Normalised total kidney volume could be estimated easily by measuring the kidney dimensions by ultrasound, using an ellipsoid formula and dividing the result by the patient's BSA. This volume showed a moderate correlation with kidney

function tests, but did not, however, correlate with the incidence of proteinuria or albuminuria. Bilaterally, small kidneys might be associated with a risk of hypertension.

According to recent guidelines [25], prophylactic antibiotic therapy is no longer recommended after febrile UTI, and there therefore seems to be no need to search systematically for VUR in UTI patients. There is evidence, however, that renal injury may be associated even with mild or moderate vesicoureteral reflux [14]. Some authors have already expressed fears that the application of these new protocols might cause a lack of prevention of kidney damage in children with VUR [26]. We found here that even low-grade VUR has long-term consequences. Since ultrasound measurements of kidney size and kidney function in middle-aged patients correlate with earlier VUR, the measuring of kidney size in early adulthood by ultrasound could probably predict the development of renal deterioration and the risk of hypertension in later life. Clinicians should pay attention to these patients and include a competent ultrasound examination, BP measurement and GFR at some appropriate period when further renal growth ceases.

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