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OUTCOME OF ANTENATALLY DETECTED URINARY TRACT ANOMALIES

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ACADEMIC DISSERTATION

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To my family, with love and gratitude

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1. SUMMARY

The advent of obstetric ultrasonography (US) has enhanced the early detection of various urinary tract anomalies. The widespread use of routine obstetric US has also substantially increased the number of patients detected with urinary tract anomalies. The objective of this research project was to clarify the long-term outcome of patients with antenatally detected urinary tract anomalies and to investigate whether the outcome of these patients differs from that of patients with postnatally detected conditions.

The study population comprised 51 patients with vesicoureteral reflux (VUR), 48 with a multicystic dysplastic kidney (MDK), 46 with posterior urethral valves (PUV), and 68 with pelviureteric junction (PUJ) obstruction. In the studies of VUR, MDK, and PUV, anomalies were detected either antenatally (21 cases with VUR, 37 with MDK, 23 with PUV) by using obstetric US or postnatally during the neonatal period (cases with VUR) or during infancy. The one study of cases with PUJ obstruction included only patients whose conditions were detected antenatally. Of the total of 213 study patients, 209 were diagnosed and treated at the Hospital for Children and Adolescents, University of Helsinki, between 1983 and 1999, and 4 PUV patients at the Department of Pediatrics, Tampere University Hospital, between 1983 and 1997. The long-term outcome of all patients was retrospectively analyzed, and in cases with VUR and PUV, the outcome of antenatally detected patients was compared with that of postnatally detected symptomatic patients. Furthermore, patients with PUV were invited to outpatient visits to determine the current status of their urinary tract and kidney function; 17 patients agreed to participate and were prospectively studied.

In cases with fetal VUR, significantly more bilateral dilating VUR was found in neonatally than in antenatally diagnosed patients (53% vs. 29%, $p=0.05$). Fourteen percent of patients presented with congenital renal dysplasia. Focal scars developed during follow-up in 19% of renal units, explicitly in dilating VUR and only in neonatally detected cases ($p<0.005$). For MDK, ultrasonographic follow-up showed involution in 13 cases (27%), whereas in 35 cases (73%) the renal conglomerate persisted throughout the study period; 32 of these patients eventually underwent nephrectomy. In involuted cases, the size of the affected

mass was significantly smaller throughout the study period than in those undergoing nephrectomy. The difference between the two groups increased continuously during follow-up, the mean involution rate being 2.5 cm/year versus 0.6 cm/year up to 18 months ($p<0.0001$). In cases with PUV, the renal outcome was poor (GFR < 60ml/min/1.73m^2) in 14 patients (30%). The poor outcome was associated with a significantly higher nadir serum creatinine value during the first year of life ($p<0.001$), with bilateral VUR ($p<0.005$), and with breakthrough urinary tract infections (UTIs) ($p<0.05$). The long-term outcome of antenatally detected cases did not differ from that of postnatally detected cases ($p=0.25$). Among the conservatively treated cases with unilateral PUJ obstruction, none of the patients' good renal function deteriorated during follow-up. In the early-operated group, primary good function remained unchanged in all. In some cases, moderate renal function improved after early pyeloplasty, whereas in cases with poor function no improvement occurred. In cases who underwent late pyeloplasty, primary good function remained unchanged. In all except one patient with bilateral obstruction treated conservatively, both the grade of hydronephrosis and split renal function remained unchanged.

In conclusion, several demographic features of fetal VUR differ from each other, depending on whether VUR is detected antenatally or postnatally. Renal damage may be of congenital origin or it may be acquired secondarily to UTI. The risk of acquired renal scarring is particularly high if dilating VUR is not detected until neonatally after the first UTI. Of patients with MDK, involution occurs in approximately one-fourth, usually within 14 months. When surgery is to be performed, the age of 2 years is recommended. In patients with PUV, poor long-term outcome is associated with bilateral VUR and with breakthrough UTIs. The nadir serum creatinine value during the first year of life is a valuable parameter for assessing the long-term outcome. The outcome of patients with antenatally detected PUV does not differ from that of patients with a postnatally detected condition. Unilateral PUJ obstruction is mostly a benign condition with good outcome. Pyeloplasty may be indicated in selected cases. A portion of the cases with bilateral PUJ obstruction can be followed conservatively.

2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles referred to in the text by Roman numerals I-IV:

I. Ylinen E, Ala-Houhala M, Wikström S. Risk of renal scarring in vesicoureteral reflux detected either antenatally or during the neonatal period. *Urology 61: 1238-1243, 2003.*

II. Ylinen E, Ahonen S, Ala-Houhala M, Wikström S. Nephrectomy for multicystic dysplastic kidney: if and when? *Urology 63: 768-772, 2004.*

III. Ylinen E, Ala-Houhala M, Wikström S. Prognostic factors of posterior urethral valves and the role of antenatal detection. *Pediatric Nephrology 19: 874-879, 2004.*

IV. Ylinen E, Ala-Houhala M, Wikström S. Outcome of patients with antenatally detected pelviureteric junction obstruction. *Pediatric Nephrology 19: 880-887, 2004.*

Some previously unpublished data are also presented.

3. ABBREVIATIONS

^{51}Cr-EDTA	^{51}chromium-ethylenediamine tetra-acetic acid
CRF	chronic renal failure
CRP	C-reactive protein
DMSA	renal scanning using ^{99m}technetium-dimercaptosuccinic acid
DTPA	renal scanning using ^{99m}technetium-diethylenetriamine penta-acetic acid
ESRD	end-stage renal disease
GFR	glomerular filtration rate
IVU	intravenous urography
MAG-3	mercaptoacetyl triglycine
MDK	multicystic dysplastic kidney
PN	pyelonephritis
PUJ	pelviureteric junction
PUV	posterior urethral valves
US	ultrasonography
UTI	urinary tract infection
UVJ	ureterovesical junction
VCUG	voiding cystourethrography
VUR	vesicoureteral reflux

4. INTRODUCTION

Antenatally performed ultrasonography (US) has dramatically changed the approach to congenital anomalies, particularly those involving the genitourinary tract. The first report of antenatal detection of a fetal urologic anomaly dates back to 1970 (Garrett et al. 1970). Since then, ultrasonographic evaluation of the fetus has developed considerably, and the number of fetuses identified with known or suspected urinary tract anomalies has increased markedly. Reported incidences of antenatally detected congenital anomalies affecting the genitourinary system have varied from 0.25% to 1.43% of live births (Helin and Persson 1986, Livera et al. 1989, Rosendahl 1990, Gunn et al. 1995, James et al. 1998). The most common finding is hydronephrosis, which accounts for up to 50% of all abnormalities detected during the antenatal period (Saari-Kemppainen et al. 1990, Blyth et al. 1993, Lama et al. 1996).

Most patients with an antenatally detected urinary tract anomaly can be managed conservatively pre- and postnatally. In some cases, intrauterine intervention has been attempted, but the results have not been promising. Conservatively treated patients need regular follow-up, and antimicrobial prophylaxis is often indicated. In cases where renal function is poor or is at risk of declining, surgical treatment is warranted. In a few patients, the kidneys may deteriorate despite attempts at salvage. These patients eventually require kidney transplantation.

The greatest advantage of antenatal detection is that the examinations and treatment needed can be offered immediately after birth, before possible permanent damage due to e.g. urinary tract infection develops. On the other hand, the widespread use of routine antenatal US has significantly altered the detection and mode of presentation of many urological anomalies. Consequently, pediatrics and pediatric urologists are now confronted with a large number of infants with asymptomatic urinary tract malformation. Finding, for instance, hydronephrosis in the fetus may encourage treatment of an abnormal-appearing kidney that might otherwise remain asymptomatic for a lifetime. Furthermore, the relative frequency with which hydronephrosis is found can lead to considerable parental anxiety

and utilization of medical resources. Hence, the frequent finding of fetal hydronephrosis presents both an opportunity and a dilemma.

5. REVIEW OF THE LITERATURE

5.1. ANTENATAL ULTRASOUND

The first report on the use of US in pregnancy was published in 1958 (Donald et al. 1958). Ultrasonographic evaluation of the fetus has since developed considerably. During the last few decades the use of fetal US has increased dramatically, and several countries have instituted programs for routine antenatal screening. With the aid of antenatal US, gestational age can be determined, multiple pregnancies detected, fetal growth followed, and perhaps most importantly, congenital malformations identified. US has become an essential component of fetal evaluation, allowing antenatal counselling, prompt transfer to units specializing in newborn care, and appropriate treatment after birth.

Congenital malformations occur in 2% to 3% of all infants (Ash et al. 1977, Reddy and Mandell 1998). With antenatal US, congenital malformation is detected in 0.5% to 2.4% of fetuses (Jassani et al. 1982, Helin and Persson 1986, Rosendahl and Kivinen 1989, Chitty et al. 1991, Levi et al. 1995). Reported sensitivities of antenatal US in detecting congenital anomalies range from 8.7% to 83.0% (Campbell and Pearce 1983, Rosendahl and Kivinen 1989, Chitty et al. 1991, Saari-Kemppainen et al. 1994, Skupski et al. 1996). The wide range in reported sensitivity is mostly due to some of the screening studies being conducted among the general population (Rosendahl and Kivinen 1989, Saari-Kemppainen et al. 1990, Chitty et al. 1991, Skupski et al. 1996, Grandjean et al. 1999) and others in high-risk populations (Campbell and Pierce 1983, Sabbagha et al. 1985). Different classifications and exclusion criteria of anomalies also influence the results. The frequency of US performed during pregnancy, the time of gestation when US is performed, and the skill and technique of the ultrasonographer may also vary, causing discrepancy in results. Specificity of antenatal US has been reported to be almost 100% (Rosendahl and Kivinen 1989, Chitty et al. 1991, Goncalves et al. 1994, Carrera et al. 1995).

5.2. ANTENATAL DETECTION OF FETAL UROLOGICAL ANOMALIES

At present, many of the urinary tract anomalies are detected in utero. The incidence of antenatally detected urinary tract anomalies has been reported to lie between 0.25% and 1.43% (Helin and Persson 1986, Livera et al. 1989, Rosendahl 1990, Gunn et al. 1995, James et al. 1998). Patients with urinary tract anomalies frequently also have other anomalies (Cendron et al. 1996).

In antenatal US examination, fetal kidneys and bladder can be visualized as early as in 10 to 12 weeks of gestation, and most kidneys are identified by the 18^{th} week (Saphier et al. 2000). Although some urinary tract anomalies may be identified in the 12^{th} to 14^{th} week of gestation, an accurate assessment cannot be made until after the 16^{th} to 18^{th} week of gestation because before this it is impossible to distinguish the cortex, medulla, and central echo in the renal sinus representing the pelvis (Elder and Duckett 1988, Bronshtein et al. 1990). Many of the anomalies today are detected before the 20^{th} week of gestation; however, the detection rate increases with fetal age (Kullendorff et al. 1984, Helin and Persson 1986, Rosendahl and Kivinen 1989, Economou et al. 1994). In the US examination, a normal renal collecting system (calyces and pelvis) should not be seen, and a visible renal pelvis is indicative of hydronephrosis (Centron et al. 1996). Diagnostic criteria for significant fetal hydronephrosis have, however, remained controversial. Normal fetal ureters and urethra are not generally seen. Cystic lesions are easily identified on US examination, but could be confused with dilated renal calyces. Dilated calyces (caliectasis) has been found to correlate well with functionally significant obstruction (Coplen 1997). Cortical cysts and echogenic parenchyma suggest that dysplasia and severe renal damage may be present (Coplen 1997). Renal function of the fetus can also be estimated by the amount of amniotic fluid detected by US. Oligohydramnios is an accurate reflection of decreased urinary output and the most important measure of renal impairment. A normal amniotic fluid volume indicates that at least one renal unit is functioning (Lama et al. 1996).

The most common antenatally detected urinary tract anomalies are pelviureteric junction (PUJ) obstruction, multicystic dysplastic kidney (MDK), renal duplication, posterior urethral valves (PUV), obstructed or nonobstructed megaureter, vesicoureteral reflux

(VUR), transitional urinary tract dilatation, and renal agenesis. Other urinary tract anomalies include ectopic ureter, ureterocele, Prune Belly syndrome, extrarenal pelvis, megacystis-megaureter syndrome, urethral aplasia, polycystic kidney disease, and a simple renal cyst. In antenatal differential diagnostics, megacalicosis, ovarian cyst, hydrocolpos, sacrococcygeal teratoma, bowel duplication, duodenal atresia, and anterior meningocele should also be taken into consideration as a possible, albeit rare, causes of hydronephrosis (Lama et al. 1996, Elder 1997).

In the past, children with urinary tract anomalies were identified either during physical examination carried out because of a palpable mass or when a complication, such as infection, bleeding, or the development of kidney stones, occurred. Approximately 80% of neonates with an antenatal diagnosis of urinary tract abnormality have no signs or symptoms at birth (Thomas and Gordon 1989). Thus, antenatal US enhances the detection of potentially significant urinary tract anomalies before postnatal onset of symptomatic disease, which allows diagnostic evaluation and appropriate treatment to be given before complications occur.

5.3. ANTENATAL DETECTION OF HYDRONEPHROSIS

Hydronephrosis is recognized in US examination as a dilatation of the renal pelvis, usually associated with dilatation of the calyces. Hydronephrosis can be unilateral or bilateral. The ureters and bladder may also be dilated. The incidence of hydronephrosis detected by antenatal US has been reported to be 1 per 100 pregnancies, but only 1 in 500 represents a significant urological problem (Thomas 1990). The incidence of hydronephrosis varies according to the study depending upon the criteria applied and the timing of US. The degree of hydronephrosis varies based on the stage of pregnancy and the underlying etiology. Measurement of the anteroposterior diameter of the intrarenal pelvis in a transverse plane is the simplest and most commonly used technique for ultrasonographic diagnosis of hydronephrosis. There is, however, no consensus on the measurements for a normal renal pelvis. A renal pelvic anteroposterior diameter of 10 mm was earlier considered the cut-off between normal and abnormal (Grignon et al. 1986, Cendron et al.

1996). However, primary VUR was often missed using a cut-off point this high. It has subsequently been proposed that infants with a renal pelvic anteroposterior diameter over 4 or 5 mm in antenatal US should be investigated postnatally (Jaswon et al. 1999, Saphier et al. 2000).

In many cases, antenatally detected hydronephrosis will resolve either before birth or during the first year of life, but in some cases the hydronephrosis grade remains stable or even increases. In the majority of patients, renal function will develop normally after birth despite the possible persistence of hydronephrosis. Surgical intervention is, however, sometimes necessary to avoid deterioration of renal function.

5.4. ANTENATAL INTERVENTION FOR URINARY TRACT ANOMALIES

Intrauterine surgery was introduced with optimism. Reports concerning fetal surgery have not, however, been promising. The two basic objectives of intrauterine intervention in a fetus with a urinary tract anomaly are 1) to restore sufficient amniotic fluid to allow normal pulmonary development, and 2) to prevent renal dysplasia. Nevertheless, experimental and clinical evidence indicate that both renal dysplasia and pulmonary hypoplasia may be irreversible by the time the urinary tract dilatation is first noted by antenatal US (Coplen 1997).

Prenatal intervention is mainly limited to male fetuses with early obstruction due to PUV. In the early 1980s, open fetal surgery was performed in some cases with obstructive uropathy, but the results were quite poor. Vesicoamniotic shunt placement has also been used since the early 1980s, with Golbus et al. describing the first case in 1982. Complications occur in nearly half of all patients, the overall survival ranging from 22% to 62% (Manning et al. 1986, Elder et al. 1987, Coplen 1997, Freedman et al. 1999, Holmes et al. 2001).

In some recent studies, percutaneous fetal cystoscopy has been used in fetal intervention with good results. This technique allows direct visualization and evaluation of the course

of obstruction, and in cases with PUV, mechanical or laser ablation can be performed (Quintero et al. 1995, 2000).

5.5. PELVIURETERIC JUNCTION (PUJ) OBSTRUCTION

Pelviureteric junction obstruction is the most common cause of antenatal and neonatal hydronephrosis. With the use of routine obstetric US, hydronephrosis suspected of being caused by PUJ obstruction is observed in approximately 1 in 1000 live births (Cendron et al. 1996). The obstruction in the junction between the pelvis and the ureter can be caused by a variety of either intrinsic or extrinsic anatomical or functional abnormalities that restrict urinary flow. Intrinsic obstruction may be due to focal narrowing at the junction between the pelvis and the ureter or by segmental areas of abnormal peristalsis (Koff 1999). Extrinsic obstruction may be caused by kinks, angulations, or aberrant vessels. Obstruction is usually partial, and the condition may vary in its severity. Renal function on the affected side can be either normal or reduced (Koff and Wise 1996).

Obstruction has been proposed to be defined as ”any restriction to urinary outflow which if untreated will injure the kidney” (Koff 1987). Peters (1995) suggested that obstruction be defined as any restriction in urinary drainage that impairs the functional potential of the kidney. In the newborn, however, it is difficult to assess the significance of an obstruction to urinary flow because the newborn kidney displays anatomic and functional immaturity. At birth, there is a significant depression in renal function. Thereafter, renal function improves quickly as the kidney grows and as changes occur in renal vascular resistance and renal perfusion (Koff 1998). Consequently, hydronephrosis in the newborn has the potential for spontaneous improvement or resolution with maturation, if no significant obstruction is present.

Earlier, infants with PUJ obstruction were detected because of an abdominal mass, whereas pain, hematuria, or UTI was commonly seen in older children (Koff and Wise 1996). At present, 30% to 50% of patients are discovered in utero as a result of antenatal US screening (Cendron et al. 1996). PUJ obstruction usually occurs unilaterally. In 10% to

40% of patients, the disease has been reported to be bilateral (Koff and Wise 1996, Reddy and Mandell 1998). In unilateral cases, the left kidney is 1.5-3 times more likely to be affected. Males predominate, the M/F ratio being 1.8-2.8:1 (Cartwright et al. 1992, Salem et al. 1995, Cendron et al. 1996, McAleer and Kaplan 1999, Subramaniam et al. 1999). Although the occurrence of PUJ obstruction is mostly sporadic, familial tendency has been observed (Atwell 1985). Coexisting abnormalities, especially genitourinary, do occur, the prevalence of e.g. VUR being 15% (Cendron et al. 1996). Voiding cystourethrography (VCUG) is recommended in cases with PUJ obstruction. The association between MDK and contralateral PUJ obstruction is well-known, with the dysplastic kidney possibly reflecting the extreme end of the clinical spectrum of PUJ obstruction (Reddy and Mandell 1998).

In US examination, PUJ obstruction can be suspected when hydronephrosis is present without a dilated ureter and bladder. The degree of renal pelvic and calyceal dilatation and thickness of the renal cortex may vary. The initial postnatal US performed within the first few days of life may appear normal despite significant obstruction due to oliguria. When hydronephrosis has been detected antenatally, renal US examination should be repeated (Cendron et al. 1996). In many cases, PUJ obstruction may result in clinically apparent but functionally insignificant dilatation of the upper urinary tract. Although ultrasonographic examination is the cornerstone of screening for PUJ obstruction, the degree of hydronephrosis has not proved to be a good indicator for the presence of obstruction. Currently, no single test can reliably predict whether a hydronephrotic kidney will deteriorate or improve. Excretory urography (IVU) has traditionally been the method used to evaluate hydronephrosis, but it has significant limitations in neonates. Renal isotope scan with either ^{99m}technetium-diethylenetriamine penta-acetic acid (DTPA) or mercaptoacetyl triglycine (MAG-3) is now most widely used to assess the presence or absence of obstruction. In a renal isotope scan, split renal isotope uptake and isotope washout pattern and half time can be measured. Each of these parameters has its own limitations and is unable to accurately assess whether significant obstruction is present. The washout curve is subject to many variables in the newborn, including transitional low glomerular filtration rate (GFR). The deterioration in split renal isotope uptake during follow-up has been suggested to be the only reliable proof of the presence of obstruction (Koff 1998, Ulman et al. 2000). Magnetic resonance urography, which combines anatomic

and functional information, has recently been found to be a promising imaging modality in assessing patients with hydronephrosis; reports concerning its clinical use are still, however, quite limited (Leppert et al. 2002, Perez-Brayfield et al. 2003).

When surgery is considered necessary, a PUJ obstruction is corrected by performing a pyeloplasty, in which the pelviureteric junction is excised and the ureter and renal pelvis are reattached. A dismembered Anderson-Hynes pyeloplasty is usually performed. Much controversy, however, exists about the indications and optimal timing of surgical treatment. Some surgeons advocate early pyeloplasty to optimize renal development and function by preventing long-term exposure to obstruction (King et al. 1984, DiSandro and Kogan 1998, Palmer et al. 1998, Zupancic et al. 2002). Others favor observation and late pyeloplasty only if renal function decreases in the affected side or the patient becomes symptomatic (Ransley et al. 1990, Blyth et al. 1993, MacNeily et al. 1993, Koff and Campbell 1994).

The outcome of patients with PUJ obstruction is often good because function of the contralateral kidney is usually normal. In most cases of antenatally detected unilateral PUJ obstruction, the outcome of the affected side is favorable as well; hydronephrosis does not progress, renal function does not deteriorate, and subsequent surgery is not required (Koff 1998). Patients with bilateral PUJ obstruction are naturally at greater risk for poor outcome (Saphier et al. 2000).

5.6. MULTICYSTIC DYSPLASTIC KIDNEY (MDK)

Multicystic dysplastic kidney is a congenital anomaly and is the second most common cause of abdominal mass in the newborn (Cendron et al. 1996). The first description of MDK found at autopsy is by Cruveilhier in 1836 (Bloom and Brosman 1978). A hundred years later, Schwartz identified and removed MDK during a surgical exploration (Robson et al. 1995). In 1955, Spence suggested that MDK be considered an entity apart from polycystic kidney disease and other cystic disorders.

While the etiology of MDK is unconfirmed, it is thought that either early obstruction of the ureteric bud leads to dysplasia or dysplasia is a primary condition associated with ureteric bud and nephrogenic blastomal abnormalities (Beck 1971). In MDK, the renal parenchyma is replaced by nonfunctioning, noncommunicating cysts of variable size. The normal pelveocalyceal system is absent, and the proximal ureter is atretic or nonpatent (Gordon et al. 1988).

MDK usually develops in a population sporadically. It has, however, been reported as a feature of some inherited syndromes and chromosomal disorders and also to manifest in siblings (Zerres et al. 1984, Moazin et al. 1997). Furthermore, a recent report documents an inheritance pattern in three affected families (Belk et al. 2002). Exposure to teratogens has also been claimed to be a cause of MDK in some cases (Robson et al. 1995). The risk of MDK among babies of both pregestational and gestational diabetic mothers is increased (Ylinen and Wikström 2002).

MDK is usually unilateral, the left side more frequently being affected (Robson et al. 1995). However, MDK may be bilateral, which usually results in stillbirth or death within the first few hours of life due to accompanying pulmonary hypoplasia (Dungan et al. 1990, Robson et al. 1995). The incidence of unilateral MDK has been estimated to be 1 in 4100-4300 live births, and the combined incidence of unilateral and bilateral MDK 1 in 3600 births (Gordon et al. 1988, Ylinen and Wikström 2002). Males are slightly more often afflicted than females (Robson et al. 1995).

Unilateral MDK is commonly associated with malformations of both the upper and the lower urinary tract. Anomalies of the contralateral kidney are present in 22% to 53% of patients with MDK (Greene et al. 1971, Sapin et al. 1994, Kessler et al. 1998, Perez et al. 1998). The most frequently associated anomaly is VUR, which occurs in 9% to 43% of patients (Wacksman and Phipps 1993, Karmazyn and Zerin 1997, John et al. 1998, Kessler et al. 1998, Perez et al. 1998).

Until recently, MDK was typically discovered in a postnatally performed physical examination. However, most MDKs are not palpable at birth (Cendron et al. 1996). Today, MDK is usually detected antenatally during routine obstetric US examination. US has been

shown to be advantageous in the diagnosis and follow-up of MDK and also in detecting any associated anomalies. Renal isotope scan (DMSA, DTPA, or MAG-3) is the preferred instrument to prove the absence of function of MDK, thus confirming the diagnosis. A VCUG study is recommended to be performed on all patients with MDK because of the increased incidence of associated VUR (Cendron et al. 1996).

The management of MDK is still controversial. Earlier, the routine treatment was nephrectomy, which established the final diagnosis. At present, conservative management is favored because the natural history of MDK is now better known and recent reports have shown that a significant number of kidneys with MDK will undergo spontaneous involution (Wacksman and Phipps 1993, Oliveira et al. 2001). There is, however, considerable variation in the reported involution rates of MDK, ranging from 10% to 75% (Vinocur et al. 1988, Orejas et al. 1992, Strife et al. 1993, Wacksman and Phipps 1993, Sukthankar and Watson 2000, Oliveira et al. 2001).

Patients with unilateral MDK are usually asymptomatic. Such complications as malignancy, hypertension, pain, and UTI have been related to MDK. A review of the literature identified some 18 cases of malignancy associated with MDK, including 11 cases of Wilms' tumor in pediatric patients, with the remainder mostly displaying adult-type renal adenocarcinoma (Perez et al. 1998, Mingin et al. 2000). The risk of Wilms' tumor arising in MDK has been estimated to be 3- to 10-fold that of the general pediatric population (Perez et al. 1998, Beckwith 1992). Nineteen cases of hypertension have been associated with MDK (Husmann 1998, Snodgrass 2000). In only 7 of the 18 cases subjected to nephrectomy, however, did hypertension become resolved. Ambrose et al. (1982) described several adult patients who had experienced pain and urinary infection. However, in other studies, the reported frequencies of UTIs have been similar to those of children without MDK (Feldenberg and Siegel 2000, Oliveira et al. 2001)

The outcome of patients with unilateral MDK as the only malformation is generally expected to be good. Because the ipsilateral kidney is nonfunctioning, the prognosis depends on the contralateral kidney. In patients with unilateral MDK, the contralateral kidney usually grows compensatorily to take care of renal function. Compensatory renal growth has been suggested to start in utero and continue after birth, the largest increase in

length occurring during the first six months (Glazebrook et al. 1993, Mandell et al. 1993, John et al. 1998). In many studies, renal function has been reported to be normal in patients with unilateral MDK, but in some studies serum creatinine has been noted to be slightly elevated in patients with MDK (Orejas et al. 1992, Heymans et al. 1998, Rudnik-Schöneborn et al. 1998, Kuwertz-Broeking et al. 2004). The outcome of patients with MDK associated with other significant urinary tract anomalies is less promising (Feldenberg and Siegel 2000).

5.7. VESICOURETERAL REFLUX (VUR)

Vesicoureteral reflux is an abnormal condition, in which urine flows in a retrograde direction from the bladder into the upper urinary tract. Normally, the ureters enter the bladder at an oblique angle, and the intramural section of the ureter acts as a flap-valve mechanism as the bladder fills, preventing urine from backing up and returning into the ureters. The valve-like action creates an important barrier that keeps the kidney free of bacteria and prevents the high pressure of a filled or micturating bladder to affect the ureter and the kidney (Rushton 1999). Anatomic or functional abnormality of the normally competent ureterovesical junction can lead to VUR (Decter 2001). VUR can be primary or secondary. Primary VUR is congenital and is not associated with any underlying neuromuscular or obstructive phenomenon. Primary VUR is assumed to be due to an early malformation in the ureteric bud, which can lead to the development of a shorter intramural section of the ureter, compromising its ability to act as a flap valve (Mackie et al. 1975, Belman 1997). Secondary VUR occurs in the presence of a bladder outlet obstruction or abnormal bladder function, including neurogenic bladder. VUR can also be transient, occurring in a normal urinary tract during and immediately after acute UTI (Jones and Asscher 1992).

Primary VUR is the most common congenital anomaly of the urinary tract. The true prevalence of VUR in healthy infants and children is unknown, but it has been estimated to be less than 1% (Jacobson et al. 1999). VUR is usually diagnosed in connection with UTI. Consequently, most studies concerning the frequency of VUR are performed on patients

suffering from UTI, VUR being found in 25% to 40% of these patients (Blickman et al. 1985, Jodal 1987, Merrick et al. 1995). With the advent of routine obstetric US, some of the patients are now detected antenatally. In 4% to 28% of cases, antenatally detected hydronephrosis has been reported to be due to VUR (Najmaldin et al. 1990, Ring et al. 1993, Gunn et al. 1995, Anderson et al. 1997, MacIlroy et al. 2000, Brophy et al. 2002). VUR diagnosed in the evaluation of antenatally detected hydronephrosis is often of high grade and occurs more frequently in boys than in girls (Gordon et al. 1990, Boachrine et al. 1996). Clinically presenting VUR, by contrast, is more common in girls (Winberg et al. 1974, Blickman et al. 1985, Bisset 1987, Jodal 1987, Skoog et al. 1987). In antenatally detected patients, especially in male infants, VUR is primarily thought to be anatomic in origin, whereas in older girls voiding dysfunction and detrusor instability are well recognized as assisting factors in the etiology of VUR (Gordon et al. 1990, Snodgrass 1991, Sillen 1999). However, some studies suggest that bladder dysfunction and high intravesical pressure may have a contributory role in male infants with high bilateral VUR (Sillen et al. 1992, Capitanucci et al. 2000).

The etiology of VUR involves a substantial genetic component, supported by the observation that VUR is frequently found in multiple members of the same family (Scott et al. 1997, Devriendt et al. 1998, Mak and Kuo 2003). The likelihood that the sibling of a child with VUR will prove to have reflux is 27% to 42% (Noe 1992, Kenda and Zupancic 1994, Wan et al. 1996). The risk of VUR in offspring of parents with reflux is also increased compared with the general population (Noe et al. 1992).

VUR can be diagnosed most accurately by conventional radiopaque VCUG, where the severity of VUR can be graded according to the appearance of the ureters and calyces. The severity of VUR is dependent on the length of the submucous tunnel, the diameter and location of the ureteral opening, and the voiding pressure within the bladder (Anand et al. 1991). The use of several different classifications in the past has led to confusion. At present, the most widely accepted grading system is that of the International Classification, which grades VUR from I to V (Lebowitz et al. 1985). In VUR follow-up, isotope VCUG is also useful (Fretzayas et al. 1984, Polito et al. 2000b). Furthermore, contrast-enhanced voiding urosonography has recently been found to be have promise in the follow-up of VUR (Darge et al. 2002, Uhl et al. 2003).

In 1960, Hodson and Edwards first demonstrated the association between VUR and renal scarring. VUR alone does not impact renal function. Refluxing urine can, however, transport bacteria from the lower urinary tract towards the kidneys, thus predisposing the patients to pyelonephritis (PN) and renal damage. Hodson et al. (1975) found that VUR and PN alone does not cause renal damage, but intrarenal reflux in combination with bacilluria permits invasion of the renal parenchyma by bacteria, which was also confirmed by Ransley and Risdon (1978). Intrarenal reflux refers to retrograde passage of urine from the renal pelvis into the collecting tubules. Today, VUR is widely recognized to be a significant risk factor for both the development of recurrent PNs and progressive renal scarring (reflux nephropathy) (Jodal 1987, Anand et al. 1991, Smellie et al. 1992, Wennerström et al. 2000, Nuutinen and Uhari 2001, Sweeney et al. 2001). Up to 50% of patients with PN and VUR have been reported to show evidence of renal parenchymal scarring (Jodal 1987, Anand et al. 1991, Smellie et al. 1992, Sweeney et al. 2001). The extent of scarring is proportional to the severity of VUR (Winter et al. 1983, Smellie et al. 1985, Jodal 1987, Weiss et al. 1992, Stokland et al. 1996), and the frequency of scarring is related to the number of recurrent episodes of breakthrough UTIs (Jodal 1987). In addition, in several reports, the risk of renal scarring has varied according to the patient's age, with infants under 1 year being at the highest risk and those older than 5 years at the lowest (Gleeson and Gordon 1991, Martinell et al. 1995). However, in the study of Benador et al. (1997), the development of renal scars was found to be independent of children's age.

Fetal VUR diagnosed in conjunction with the antenatal detection of hydronephrosis in US examination is associated with congenital renal damage. Renal scarring has been reported to occur in up to 40% of patients with antenatally detected VUR before developing any UTI (Ring et al. 1993, Marra et al. 1994, Assael et al. 1998, Sweeney et al. 2001). The cause of congenital renal damage remains uncertain. It has, however, been speculated whether VUR operating in utero interferes with metanephric differentiation or whether congenital renal dysplasia and VUR are separate expressions of a malformed urinary tract, frequently coexisting, but not necessarily causally related (Risdon et al. 1993).

Most VUR are known to resolve spontaneously during childhood due to ”maturation” of the vesicoureteral valve. Controversy exists, however, about indications and optimal

timing of surgery. The most commonly used treatment modes are conservative follow-up by using low-dose antimicrobial prophylaxis, surgical endoscopic treatment, and ureteral reimplantation. The surgical correction of VUR eliminates the possibility of infected urine reaching the renal parenchyma, while medical treatment with chemoprophylaxis aims to prevent urine from becoming infected. Conservative management is currently favored as the primary mode of treatment because spontaneous cessation rates of severe VUR have been found to reach 40% to 60% in many studies, with resolution of lower grades of VUR being even better (Ring et al. 1993, Huang and Tsai 1995, Assael et al. 1998, Herndon et al. 1999, Farhat et al. 2000). A well-known alternative to long-term antimicrobial prophylaxis and open surgery is an endoscopic subureteric injection of tissue-augmenting substances. Dextranomer/hyaluronic acid copolymer, polytetrafluoroethylene paste, and collagen are described to successfully eliminate VUR in 60-90% of patients (Puri et al. 1995, Reunanen 1995, Kumon et al. 1997, Läckgren et al. 1999, Puri et al. 2003). In many centers, ureteral reimplantation is undertaken only in patients with severe VUR or in those with recurrent UTIs, poor compliance, or renal scarring. By contrast, Yu et al. (1997) advocated early antireflux surgery since they observed that renal units with reflux nephropathy are susceptible to UTI and new scar formation. However, in studies, including the International Reflux Study, where the frequency of renal scars in surgically versus medically treated patients has been compared, no difference has been observed (Anonymous 1987a, Smellie et al. 1992, Piepsz 1998, Smellie et al. 2001, Wheeler et al. 2003).

Impairment of growth and scarring of exposed kidneys are the main types of morphological damage associated with VUR. Reflux nephropathy can result in end-stage renal disease (ESRD), hypertension, or both. In approximately 10% to 15% of cases, ESRD is caused by reflux nephropathy (Bailey et al. 1994, Craig et al. 2000). The incidence of renal insufficiency in patients with reflux nephropathy is approximately 10% to 14% (Jacobson et al. 1989, Zhang and Bailey 1995, Martinell et al. 1996). The risk of hypertension in patients with renal scarring varies based on the length of follow-up and the severity of scarring. In follow-up studies of children with renal scarring, 6% to 13% of children with scarring will develop hypertension (Goonasekera et al. 1996, Martinell et al. 1996). In adults, hypertension has been reported to develop in up to 38% of patients with reflux nephropathy (Zhang and Bailey 1995).

5.8. POSTERIOR URETHRAL VALVES (PUV)

Posterior urethral valves is the most common cause of obstructive uropathy involving the lower urinary tract in childhood (Smith and Duckett 1996). The anomaly occurs only in males, with the incidence of PUV estimated at 1 in 4000-8000 boys (Atwell 1983, Hutton et al. 1994). PUV has been suggested to consist of a thin congenital membrane that impedes urine outflow by obstructing or partially obstructing the posterior urethra (Smith and Duckett 1996). The exact etiology of PUV is, however, unclear. PUV is usually a sporadic disorder. There are, however, reports of PUV in siblings and twins, suggesting a partial genetic etiology (Thomalla et al. 1989, Hutton and Thomas 1994, Trembath and Rijhsinghani 2002).

Young and coworkers classified valves as type I, II, or III. Much of their orginal classification has, however, been questioned (Smith and Duckett 1996). At present, in most cases, the diagnosis of PUV is made before or at birth when a boy is evaluated for antenatal hydronephrosis. However, the sensitivity of US in detecting PUV is under 50%, and thus normal US, especially when performed early in gestation (before the 24th gestational week), does not exclude PUV (Helin and Persson 1986, Dinneen et al. 1993, Hutton et al. 1994). Before the use of antenatal US, PUV was usually detected during evaluation of UTI, weak urinary stream, abdominal mass, poor weight gain, or renal failure.

In cases with suspicion of PUV, urinary tract US should be performed as soon as possible. The diagnosis is confirmed by using VCUG, which is the gold standard and method of choice for diagnosing PUV. If the patient has a normal VCUG, then PUV is excluded. From the VCUG study, the presence of VUR can also be concurrently evaluated. A renal isotope scan (MAG-3, DMSA and/or DTPA) is helpful in many cases, giving information about the presence of renal scarring or dysplasia or secondary ureterovesical junction (UVJ) obstruction from bladder hypertrophy (Smith and Duckett 1996). Urodynamic evaluation should be performed in all PUV patients throughout childhood because bladder compliance may deteriorate over time (Kim et al. 1997, Glassberg 2001). Cystoscopy is useful both in confirming diagnosis and in treatment. To follow the renal function of patients with PUV, regular measurement of serum creatinine or cystatin C is mandatory

(Ylinen et al. 1999). If serum creatinine or cystatin C values are higher than normal, the more accurate measurement of GFR is recommended by e.g. using plasma clearance of ^{51}chromium-ethylenediamine tetra-acetic acid (^{51}Cr-EDTA). The Schwartz formula can be used for the calculation of GFR as well (Smith and Duckett 1996).

Controversy exists about the best timing and approach in treating patients with PUV. Surgical treatment may comprise primary transurethral endoscopic valve ablation alone, primary valve ablation with upper urinary tract diversion (ureterocutaneostomy or pyelostomy), or temporary vesicostomy with delayed valve ablation. Many pediatric urologists advocate primary valve ablation, reserving urinary diversion for patients who do not rapidly respond to therapy (Mitchell and Close 1996, Smith et al. 1996, Close et al. 1997, Duckett 1997). The main argument against urinary tract diversion is that a temporary defunctionalization of the bladder has an iatrogenic and deleterious effect on its later function. However, some authors favor high diversion, suggesting that it can improve renal function by preserving renal parenchyma and has no adverse effect on subsequent bladder function (Lyon et al. 1992, Jayanthi et al. 1995, Kim et al. 1996).

Patients with PUV present with a broad spectrum of clinical severity, with sequelae ranging from voiding dysfunction without renal impairment to early onset of renal failure and occasionally even death. During recent years the prognosis of PUV patients has improved significantly. Mortality has decreased from 50% to less than 5% in the last 30-40 years (Williams et al. 1973, Agarwal 1999). PUV is still, however, the most common obstructive condition causing chronic renal failure (CRF) and ESRD in children (Smith and Duckett 1996). The reported frequency of ESRD in patients with PUV varies from 9% to 47% (Warshaw et al. 1985, Parkhouse et al. 1988, Connor and Burbige 1990, Reinberg et al. 1992, Smith et al. 1996, Lal et al. 1999). The frequency of ESRD is strongly influenced by the length of the follow-up. ESRD is typically seen in two distinct age groups; in one-third of cases, ESRD develops soon after birth, and in the remaining two-thirds renal function does not deteriorate until adolescence (Smith and Duckett 1996). Late-onset renal failure was previously thought to be caused by the increased metabolic demands of puberty. Current theories include hyperfiltration, reflux nephropathy, and persistent abnormal bladder function (Karmarkar 2001). In addition to the development of treatment methods, the invention of antenatal US has been proposed to improve the

outcome of patients with PUV (Cendron et al. 1996). However, in studies where the outcome of antenatally detected PUV patients was compared with that of postnatally detected patients, no proof of better outcome in the former group was observed (Reinberg et al. 1992, El-Ghoneimi et al. 1999).

Factors claimed to be associated with a poor long-term outcome in patients with PUV include antenatal detection or presentation before the age of one year; late diagnosis; bilateral, especially dilating, VUR; injury of the detrusor muscle caused by outlet obstruction; bilateral absence of corticomedullary junction in US; recurrent UTIs; delayed achievement of urinary continence, and persistent elevation of serum creatinine after valve ablation (Tejani et al. 1986, Parkhouse et al. 1988, Hulbert et al. 1992, Denes et al. 1997, Hutton et al. 1997). On the other hand, unilateral, especially left-sided, VUR and renal dysplasia, or PUV associated with urinary ascites and perirenal urinoma or large congenital type bladder diverticula have been proposed to provide a "pop-off mechanism", resulting in preservation of renal function (Hoover and Duckett 1982, Rittenberg et al. 1988). In a recent study by Cuckow et al. (1997), however, persistent unilateral VUR with ipsilateral renal nonfunction and renal dysplasia did not seem to have a protective effect on contralateral renal function.

Renal dysplasia has been observed to be present in many of the patients with PUV (Cussen 1971, Johnston 1979, Henneberry and Stephens 1980, Hoover and Duckett 1982, Haecker et al. 2002). Although the association of PUV with renal dysplasia is well-recognized, the cause-and-effect relationship is poorly understood. Renal dysplasia has been proposed to be a primary developmental malformation of the ureteric bud (Henneberry and Stephens 1980). Alternatively, dysplasia has been speculated to be caused secondarily by high intraluminar pressure during differentiation of the metanephric blastema (Beck 1971). After birth, the renal parenchyma can be damaged further by VUR and recurrent UTIs. This damage should, however, be at least partly preventable by intensive postnatal therapy.

Urinary incontinence is a common problem in boys with PUV. The prevalence of incontinence has been reported to be as high as 81% at the age of 5 years and 54% at the age of 10 years (Churchill et al. 1983, 1990, Parkhouse et al. 1988, Connor and Burbige 1990, Smith et al. 1996). In most cases, incontinence is speculated to be due to abnormal

bladder function combined with high urine output as a result of poor concentration ability (Smith et al. 1996). The reported incidence of symptomatic voiding dysfunction after surgery ranges from 13% to 38% (Krueger et al. 1980, Churchill et al. 1983, Scott 1985, Peters and Bauer 1990). Urodynamic abnormalities remain present in 20% to 88% of PUV patients despite adequate relief of urethral obstruction (Bauer et al. 1979, Koff 1983, Parkhouse and Woodhouse 1990, Peters et al. 1990, Lopez Pereira et al. 2002).

The function of the bladder has been found to be related to the outcome of patients with PUV. In the early 1980s, Mitchell presented the concept of "valve bladder syndrome" for patients with a thick-walled, poorly compliant bladder with high resting pressures even at small urine volume, resulting in progressive hydroureteronephrosis and renal failure (Mitchell 1982). Later reports have also emphasized the association between voiding dysfunction and persistent hydroureteronephrosis and VUR, late-onset renal failure, and poor allograft survival in valve transplant patients (Parkhouse et al. 1988, Reinberg et al. 1988). The surgical treatment method chosen has also been claimed to be related to the development of bladder dysfunction. In 1997, Duckett concluded that the valve bladder was an iatrogenic phenomenon that was the consequence of supravesical diversion and not secondary to either vesicostomy or primary valve ablation. In contrast, many other studies have observed that supravesical urinary diversion has no adverse effect on bladder function (Jayanthi et al. 1995, Kim et al. 1996, Jaureguizar et al. 2000, Liard et al. 2000, Podesta et al. 2000). Jaureguizar et al. (2000) postulated that poor bladder function is probably a consequence of detrusor damage in utero and has little to do with the mode of primary treatment.

Reports concerning the outcome of renal transplantation in children with PUV have been contradictory. Some earlier studies have indicated that children with renal failure secondary to PUV show a trend towards decreased renal graft survival or function compared with children with ESRD secondary to nonobstructive etiology (Churchill et al. 1988, Reinberg et al. 1988). In these studies, authors postulate that persistent bladder dysfunction is the basis of decreased graft function. Recent studies have, however, reported no decrease in graft survival in these patients as compared with controls (Connolly et al. 1995, Salomon et al. 1997, Indudhara et al. 1998).

Impaired sexual function and reduced fertility may occur in patients with PUV. These can be caused by several factors, including cryptorchidism, vasal reflux, ejaculatory dysfunction, decreased libido and potency due to CRF, and damage to the erectal nerves of the penis (Woodhouse et al. 1989, Woodhouse 1994, Nguyen and Peters 1999, Karmarkar 2001).

5.9. OTHER ANTENATALLY DETECTABLE URINARY TRACT ANOMALIES

5.9.1. Megaureter

A megaureter is a term used to anatomically describe the wide ureter. According to the international classification scheme, a megaureter may be obstructed, refluxing, or unobstructed and not refluxing (Noe 1996). Each of these groups can be divided into two subgroups: primary megaureter, where the cause of dilatation is idiopathic, and secondary megaureter, which may be caused by urethral obstruction, bladder outlet obstruction, neurogenic bladder, polyuria, or infection (Shokeir and Nijman 2000). Primary megaureter is the second to third most common cause of hydronephrosis detected during the antenatal period and is also a common cause of hydronephrosis among young children (Brown et al. 1987, Meyer and Lebowitz 1992, Ring et al. 1993, Ebel 1998, James et al. 1998). Males are four times more frequently affected than females. Megaureter is bilateral in about 25% of cases. In unilateral cases, the left ureter is involved 1.6-4.5 times more often than the right (Shokeir and Nijman 2000). Currently, about half of the cases are asymptomatic and discovered in antenatal US (Shokeir and Nijman 2000). Spontaneous resolution of megaureter is common, and conservative management is recommended at least in cases where renal function and hydronephrosis remain stable or improve and the child remains asymptomatic (Keating et al. 1989, Baskin et al. 1994, Liu et al. 1994, Arena et al. 1998, Vereecken and Proesmans 1999). Antibiotic prophylaxis is advised, especially in refluxing megaureters (Baskin et al. 1994). If surgery is required, ureteric excisional tapering is preferred for severely dilated ureters and plication of the distal ureter for less dilated units (Shokeir and Nijman 2000).

5.9.2. Renal duplication

A duplex or duplicated system, defined as a renal unit in which the kidney has two pelvicalyceal systems, is associated with either a single ureter, bifid ureters (in which two ureters join before emptying into the bladder), or two ureters (Snyder 1996). In patients with complete duplication, two ureters are present that empty separately into the bladder, whereas in patients with partial or incomplete duplication, either a single or bifid ureter is present. In clinical practice, duplication anomalies are observed about two times more commonly in girls than in boys (Decter 1997). Ureteral duplication has been reported to occur bilaterally in up to 40% of cases. The right and left sides seem to be equally affected (Snyder 1996). There is a genetic predisposition to duplication; duplication of the ureter has a birth frequency of about 1%, and the proportion of siblings and parents of probands affected is about 12% (Carter 1984).

Patients with complete duplication of ureters commonly have VUR in the lower pole orifice (Decter 1997). VUR in duplex kidneys was previously thought to be an indication for early surgical management by using ureteral reimplantation. In recent years, however, several studies have reported that low-grade VUR (grades I to II) in a lower pole ureter has a good spontaneous resolution rate, and conservative follow-up with antibiotic prophylaxis as a primary treatment is therefore recommended (Ben-Ami et al. 1989, Lee et al. 1991). High-grade VUR (grades III to V) with severe associated nephropathy is usually managed by excision of the affected lower pole and partial or total ureterectomy of its ureter (Decter 1997).

In some cases with ureteral duplication, the upper pole ureter is ectopic. Ectopic ureters clinically present more frequently in girls than in boys, and of all ectopic ureters, 70% to 90% are associated with duplex kidneys (Chowdhary et al. 2001, Berrocal et al. 2002). The function of the upper pole in cases with ectopic orifice is often quite poor. In these patients, the upper pole is removed by an upper pole heminephrectomy, and the distal end of the upper pole ureter is treated in the same fashion (Decter 1997). In cases with favorable renal function, either a procedure that preserves the upper pole or merely

conservative follow-up is recommended (Jee et al. 1993b, El-Ghoneimi et al. 1996b, Shankar et al. 2001).

Increasing numbers of duplex systems are diagnosed antenatally by US, many of the patients being asymptomatic at least in short-term follow-up. The identification of duplication prior to the onset of complications, such as UTI, has been proposed to improve the outcome of these patients. Van Salvage and Mesrobien (1995) concluded that early recognition and treatment of duplication anomalies with hydronephrosis are efficient in preventing considerable postnatal morbidity. They found that three times as many hydronephrotic upper pole moieties were functional and could thus be preserved in the group with antenatally detected hydronephrosis as compared with patients who presented postnatally. However, in the retrospective study of Hulbert and Rabinowitz (1998), antenatal diagnosis of significant duplex system hydronephrosis did not improve the rate of segmental salvage when compared with patients who presented with symptoms at an older age.

5.9.3. Ureterocele

A ureterocele is a cystic dilatation of the intravesical submucosal portion of the ureter (Snyder 1996). A ureterocele may subtend a single system or, more commonly, the upper pole ureter of a duplex system. Ureteroceles appear 3 to 4 times more often in girls than in boys. The left side is affected more frequently than the right side, with bilaterality being present in approximately 10% of cases (Decter 1997). Due to the advent of routine obstetric US examination, the number of patients with an asymptomatic ureterocele has increased. Antenatal diagnosis of a ureterocele has been reported to decrease morbidity and potential adverse outcomes related to infection, and is associated with a decreased rate of secondary procedures (Upadhyay et al. 2002). The best approach of managing these patients is, however, controversial, different managing strategies including primary endoscopic incision, upper pole heminephrectomy with or without lower tract reconstruction, conservative management, and total nephroureterectomy (Shokeir and Nijman 2002).

5.9.4. Ectopic ureter

An ectopic ureter is characterized by an ectopic ureteric orifice outside the bladder trigone. An ectopic ureter can drain a single kidney, however, about 70% to 90% are associated with complete ureteral duplication (Chowdhary et al. 2001, Berrocal et al. 2002). Approximately one-half of female patients with ectopic ureters present with a classic history of continuous dribbling incontinence, but in some cases ectopic ureters can already be observed in utero due to concomitant hydronephrosis. Boys typically present with infectious complications (Chowdhary et al. 2001). The most frequent anomaly associated with an ectopic ureter is hypoplasia or dysplasia of the renal moiety (Borer et al. 1998, Wakhlu et al. 1998, Berrocal et al. 2002).

5.9.5. Renal agenesis

Renal agenesis is a relatively common congenital urinary anomaly that is typically diagnosed during antenatal US examination. Renal agenesis is usually unilateral but can be bilateral. Since bilateral renal agenesis is incompatible with life, its clinical significance is limited. Unilateral renal agenesis may be an isolated anomaly or may be associated with chromosomal abnormalities or a variety of nonchromosomal syndromes (Koff and Wise 1996). Most commonly, it is associated with genital anomalies, which are more frequent in females than in males. The frequency of unilateral renal agenesis is, however, slightly higher in males (Koff and Wise 1996). Of the abnormalities in the contralateral kidney, VUR predominates (Song et al. 1995, Cascio et al. 1999). The outcome of patients with unilateral renal agenesis is generally good, and they have normal longevity. However, life-long follow-up of these patients is indicated due to their increased risk of developing proteinuria, hypertension, and renal insufficiency (Koff and Wise 1996).

5.9.6. Prune Belly syndrome

Prune Belly syndrome can also be the cause of antenatally detected hydronephrosis. The syndrome is a specific constellation of anomalies consisting of an abdominal wall deficient in muscular tissue, bilateral undescended testes, and an abnormal urinary tract characterized by tortuous dilated ureters, megalocystis, dilated prostatic urethra, and renal dysmorphism (Coplen et al. 1996). The abdominal wall is lax, distended, and wrinkled. In many cases, patients also have other associated anomalies such as cardiopulmonary, gastrointestinal, and musculoskeletal abnormalities (Jennings 2000).

5.9.7. Megacystis-megaureter syndrome

The term megacystis-megaureter designates a finding of hydroureteronephrosis, a large, thin-walled bladder, and high-grade VUR. Routine obstetric US examination has increased the incidence of this syndrome, which can be predicted with reasonable accuracy antenatally (Willi and Lebowitz 1979, Mandell et al. 1992).

5.9.8. Transitional urinary tract dilatation

In many cases, urinary tract dilatation detected during the antenatal period resolves either before the end of pregnancy or within the first year of life. This transitional urinary tract dilatation has been suggested to be due to high fetal urine production, insufficient maturation of the PUJ or UVJ, or reflux of urine from the bladder to the kidney (Woodward and Frank 2002). The reported frequency of transitional hydronephrosis in patients with antenatal urinary tract dilatation has varied from 15% to 75% (Corteville et al. 1991, Blyth et al. 1993, Lam et al. 1993, Gunn et al. 1995, Sairam et al. 2001, Woodward and Frank 2002).

6. AIMS OF THE STUDY

The main objective of this study was to clarify the long-term outcome of antenatally detected urinary tract anomalies and to investigate whether the outcome of patients with an antenatally detected urinary tract anomaly differs from that of patients with a postnatally detected condition.

Specific aims of the study were:

1. to examine the demographic features and renal outcome of fetal VUR (I);

2. to evaluate criteria for a conservative versus a surgical approach in the treatment of MDK and to determine optimal timing of surgery, when indicated (II);

3. to investigate the significance of different prognostic factors and the long-term renal outcome in boys with PUV detected either antenatally or during infancy (III);

4. to clarify the long-term outcome of patients with antenatally detected PUJ obstruction treated either conservatively or operatively (IV).

7. PATIENTS AND METHODS

7.1. PATIENTS

The study groups are shown in Table 1. Patient collection was based on the hospital patient registry.

Table 1. Patient data in Studies I-IV.

Study	Diagnosis	Number of patients (antenatal/postnatal)	Mean follow-up, years (range)
I	VUR	51 (21/30)	7.4 (2.7-19.5)
II	MDK	48 (37/11)	3.8 (2.0-10.5)
III	PUV	46 (23/23)	12.5 (5.5-20.1)
IV	PUJ obstruction	68 (68/0)	7.9 (3.7-19.6)

VUR=vesicoureteral reflux, MDK=multicystic kidney, PUV=posterior urethral valves, PUJ=pelviureteric junction

Study I: The sample included patients born between 1983 and 1999 with either hydronephrosis detected antenatally by using obstetric US and confirmed postnatally to be due to VUR or VUR diagnosed after developing the first UTI during the neonatal period (before the age of 28 days). All patients were treated at the Hospital for Children and Adolescents, University of Helsinki. There were 21 antenatally detected and 30 neonatally detected patients, having 35 and 51 refluxing units, respectively. All patients were considered to represent cases of fetal VUR. Routine US examination had been performed during pregnancy on all mothers, including mothers of neonatally detected cases, with the

first examination occurring close to the 20th gestational week. In all neonatally detected cases, the result of the antenatal US examination had been considered normal. The median gestational age at detection was 29 (range 14 to 40) weeks. The median age of the neonatally detected patients presenting with symptomatic UTI was 18 (range 3 to 27) days. Patients with VUR secondary to other urinary tract malformations or due to obstructive conditions of the lower urinary tract were excluded.

Study II: The sample consisted of MDK cases born between 1989 and 1999 and treated at the Hospital for Children and Adolescents, University of Helsinki. There were altogether 48 such cases. A routine US examination had been performed during pregnancy on all mothers, with the first examination occurring close to the 20th gestational week. Thirty-seven of the cases (77%) were detected antenatally. The median gestational age at detection was 21 weeks. The median age at the time of diagnosis for the 11 postnatally detected cases was 6 days. There were 26 boys and 22 girls (M/F 1.2). All patients had unilateral MDK. The left kidney was affected in 28 cases, and the right kidney in 20 cases (L/R 1.4).

Study III: The study population comprised 46 patients with PUV detected either antenatally (23 cases) or during infancy, i.e. within the first year of life (23 cases). The sample included all patients who were diagnosed and treated either at the Hospital for Children and Adolescents, University of Helsinki (42 cases), or at the Department of Pediatrics, Tampere University Hospital (4 cases), and who were born between 1983 and 1997. Routine US had been performed during pregnancy on 40 of the 46 mothers (87%), with the first examination occurring close to the 20th gestational week. The median gestational age at detection was 28 (range 16 to 38) weeks. In the postnatally detected cases, the time of diagnosis ranged from one day to 356 days (median 31 days).

Study IV: The sample included patients with antenatally detected hydronephrosis confirmed postnatally to be due to PUJ obstruction, and who were diagnosed and treated between 1983 and 1998 at the Hospital for Children and Adolescents, University of Helsinki. The first US had been performed on all mothers close to the 20th gestational week. In many cases, repeated US examinations were performed. The median gestational age at detection was 29 (range 15 to 38) weeks. The patients comprised 47 boys and 21

girls (M/F ratio 2.2). PUJ obstruction was unilateral in 54 patients and bilateral in 14 (82 hydronephrotic units in total). In patients with unilateral PUJ obstruction, the left kidney was affected in 28 and the right in 26 cases (L/R 1.1). Patients with other urinary tract malformations were excluded.

7.2. METHODS

Antenatal and postnatal clinical records and all radiological and laboratory findings were analyzed retrospectively (I-IV). In the prospective part of the study, the patients with PUV were referred to outpatient visits, with the exception of 8 patients on dialysis or with kidney transplants, to define up-to-date status of their urinary tract and kidney function. Patients on dialysis or with kidney transplants already had up-to-date information on renal function. Of the 38 patients, 17 (45%) agreed to participate. At visits, urinary tract US, radionuclide scan (DMSA and/or DTPA), glomerular filtration rate (^{51}Cr-EDTA), and urinary flow (plus US residual) were performed. Laboratory blood tests (hemoglobin, sodium, potassium, calcium, albumin, creatinine, cystatin C) were performed and urine samples (osmolality, sodium, potassium, creatinine, protein, albumin) obtained. In addition, blood pressure, weight, and height were measured. Anamnestic data with a special focus on UTIs, achievement of urinary continence, and method of treatment were also recorded. For the remaining 21 cases, the results of the last outpatient visit, where the status of urinary tract and kidney function had been thoroughly examined, were used to determine the long-term renal outcome and the end-point of follow-up of individual patients (III).

7.2.1. Radiologic imaging studies

All patients had initially undergone an US examination within the first week of life or during the first hospitalization. Ultrasonography was repeated every 3 to 6 months during the first year and every 12 to 24 months thereafter until either resolution of hydronephrosis (I, III, IV) or complete involution of MDK or nephrectomy (II). In cases with PUJ

obstruction, hydronephrosis was graded by using the Society of Fetal Urology grading system (Kletscher et al. 1991, Fernbach et al. 1993).

Conventional radiopaque VCUG had been performed on all patients with hydronephrosis confirmed postnatally to be due to VUR and on all patients with PUV to confirm diagnosis. Furthermore, 43 of the 48 patients with MDK and 42 of the 68 patients with PUJ obstruction underwent a VCUG study to assess possible presence and grade of VUR. In refluxing cases, a follow-up isotope VCUG was performed every 6 to 24 months to evaluate the resolution of VUR. Reflux was graded according to the International Classification (Lebowitz et al. 1985).

A DMSA scan had been performed on all patients with VUR, MDK, and PUV and on 20 of the 68 patients with PUJ obstruction to detect parenchymal filling defects and split renal isotope uptake. Severely decreased function of a single renal unit was defined as a split isotope uptake of less than 30% in cases with VUR (I) or of less than 10% in cases with PUV (III). If detected at the first isotope scan and/or depicting global coexistent increased or heterogeneous echogenicity on US, the finding was considered to indicate congenital renal dysplasia. In patients with fetal VUR, isotope uptake defects were taken to indicate newly acquired renal scarring if observed at least 6 months after UTI (I).

Split renal isotope uptake and excretion were estimated in all cases with PUJ obstruction by using a DTPA scan. The diuresis was enhanced by administration of furosemide and performed using a standard protocol (Tamminen et al. 1978, Vihma et al. 1983). The DTPA scan was performed initially at 5 to 6 weeks of age and repeated every 6 to 12 months until the age of 2 years, and thereafter every 12 to 24 months if hydronephrosis had not resolved. In 3 cases with unilateral obstruction, MAG-3 was used alternatively in the initial examination.

In most cases, intravenous urography (IVU) had been performed either initially or during follow-up to delineate the morphology of the upper tract more accurately.

Urodynamic studies had been performed on all patients with PUV and also on patients for whom lower urinary tract dysfunction had been suspected.

7.2.2. Laboratory investigations

Serum creatinine had been measured initially, at regular visits, and at the end of follow-up. In patients with PUV, creatinine was measured after urethral catheter drainage for at least 3 days, after valve ablation, and thereafter during visits until the end of follow-up. GFR was measured using ^{51}Cr-EDTA clearance or calculated from the Schwartz formula, height x K/ serum creatinine, where K=0.55 for patients aged 1 to 13 years and K=0.7 for those aged 13 to 21 years (Schwartz et al. 1987). In cases with PUV, GFR had been estimated at the end of follow-up using ^{51}Cr-EDTA clearance in 40 cases and the Schwartz formula in 6 cases (III). Urine cultures were obtained at regular visits and when UTI was suspected. Blood cultures were obtained if clinically indicated. C-reactive protein (CRP) was measured when PN was suspected.

7.2.3. Blood pressure, weight, and height

Blood pressure, weight, and height had been measured initially, during visits, and at the end of follow-up in most cases. Normal blood pressure was defined as systolic and diastolic pressure of less than the 95th percentile adjusted for age, sex, and height (Anonymous 1987b).

7.2.4. Urinary continence

The achievement of urinary continence in patients with PUV was recorded. Urinary continence was defined as being totally dry during both day and night.

7.2.5. Antimicrobial prophylaxis

Low-dose antimicrobial prophylaxis using either trimethoprim or nitrofurantoin had been administered to all patients with VUR or PUV and to most patients with PUJ obstruction, initiated in antenatally detected cases within a few days of birth and in postnatal cases after detection of hydronephrosis. Prophylaxis had been continued in cases with VUR until spontaneous cessation or surgical treatment and in cases with PUV and PUJ obstruction for varying periods.

7.2.6. Urinary tract infections

Data concerning the first and recurrent and/or breakthrough UTIs were recorded. PN was defined as the combination of a positive urine culture (growth of $\geq 10^5$ bacteria/ml in two sterile-bag specimens or any growth in a suprapubic bladder aspirate) in the presence of at least two of the following three criteria: pyuria (leukocyte count >10/mm^3), fever ≥38.5 °C, or a serum CRP level of ≥40 mg/l. Cystitis was defined as a combination of a positive urine culture (growth of $\geq 10^5$ bacteria/ml in a sterile-bag specimen or any growth in a suprapubic bladder aspirate) and UTI signs and symptoms such as pyuria, low-grade fever, vomiting, and irritability.

7.2.7. Indications and modes of treatment

In cases with fetal VUR, indications for surgical treatment during follow-up were significantly decreased split isotope uptake, development of new scars, recurrent episodes of breakthrough UTIs, progressive dilating VUR (grade IV to V), and parents' request. Ten of the 21 patients in the antenatal group (48%) and 14 of the 30 neonatal patients (47%) had eventually been treated surgically. Seventeen patients had undergone ureteral reimplantation, 2 had undergone unilateral nephrectomy, and 5 had been treated endoscopically. The mean age at the time of surgery was 13.1 (range 0.5 to 39.0) months.

All MDK patients had primarily been treated conservatively. The indication for nephrectomy had been an ultrasonographically still distinguishable tissue mass, whether increased, unchanged, or decreased in size, evaluated after at least 18 months of follow-up (median 25 months). Thirty-two of the 48 patients (67%) had eventually undergone nephrectomy. The mean age at surgery was 28 months. The multicystic mass had been removed in two cases at the ages of 11 and 12 months at the parents' request. Furthermore, in two cases, the parents had refused recommended surgery. These two cases were excluded from statistical analysis.

In PUV cases, the primary surgical treatment had consisted of valve ablation alone for 23 patients. Temporary high diversion using a "ring" ureterocutaneostomy had been performed in 19, unilateral pyelostomy in two, vesicostomy in one, and bilateral end-cutaneostomies in one case. The mean age at the time of initial surgical intervention in antenatal cases was 19 (range 4 to 90) days and in postnatal cases 144 (range 4 to 365) days.

In PUJ obstruction patients, 22 of the 54 unilateral cases (41%) had been treated conservatively until the end of follow-up, 20 (37%) had undergone early pyeloplasty, and 11 (20%) late surgery. In addition, one patient had undergone early unilateral nephrectomy due to a nonfunctioning kidney. Of the 14 cases with bilateral obstruction, 9 (64%) had primarily been treated conservatively, one of which underwent late unilateral pyeloplasty. Five patients (36%) had undergone early surgery, four bilaterally and one on the worst side only. Operations had been performed due to either initially moderate or poor renal function, or deterioration in function during follow-up. Furthermore, in cases with good renal function, grade 4 hydronephrosis, grade 2 or 3 hydronephrosis with an obstructive washout pattern, persistently increasing dilatation during follow-up, PN, or recurrent abdominal pain had been indicative for surgery. The mean age for early surgery was 0.2 (range 0.1 to 0.4) years, and for late pyeloplasty 2.0 (range 0.5 to 4.7) years.

7.2.8. Definition of long-term renal outcome in cases with PUV (III)

In cases with PUV, long-term renal outcome was defined as favorable when renal function was either normal (GFR ≥90 ml/min/1.73m^2) or moderately impaired (GFR from 60 to 89ml/min/1.73m^2), and poor when the patient had either CRF or ESRD (Heilbron et al. 1991, National Kidney Foundation 2002). Chronic renal failure was defined as a stage where GFR was 59ml/min/1.73m^2 or less (National Kidney Foundation 2002). End-stage renal disease was defined as a requirement for dialysis or renal transplantation.

7.2.9. Definition of renal function in cases with PUJ obstruction (IV)

Good, moderate, and poor renal function was defined as a split renal isotope uptake of 40% or more, of 30% to 39%, and of less than 30%, respectively. In cases with bilateral PUJ obstruction, split renal function served to determine the more affected side. If no difference in split uptake was present, GFR calculated by using the Schwartz formula was used to estimate whether the kidneys showed good (normal GFR) or decreased (GFR <89ml/min/1.73m^2) function (Heilbron et al. 1991).

7.2.10. Statistical analysis

Values are expressed as means ± standard deviation (SD) unless otherwise reported. Analyses were conducted with SPSS software for Windows, Release 10.0.7 (SPSS, Inc., Chicago, IL, USA). Associations between categorical variables were examined by Fisher's exact test. Differences between continuous variables were analyzed by using Student's unpaired t-test. Student's paired t-test was used to analyze changes within groups during follow-up (IV). The Kaplan-Meier method was used to identify the rate of development of ESRD (III). Spearman's correlation was used to assess the relationship between the grade of hydronephrosis and the split renal isotope uptake in cases with unilateral PUJ obstruction (IV). Analysis of variance (ANOVA) was used to compare the mean value of

repeated measurements (II). All statistical tests were two-sided. A p-value of 0.05 or less was considered statistically significant.

7.3. ETHICAL CONSIDERATIONS

The use of patient information and the study protocols were approved by the Ethics Committees of the Hospital for Children and Adolescents, University of Helsinki, and of Tampere University Hospital. Written informed consent was obtained from the 17 patients and/or their guardians who chose to participate in the prospective part of the study after the design and purpose of the study had been explained.

8. RESULTS

8.1. DEMOGRAPHIC FEATURES OF PATIENTS WITH FETAL VUR (I)

Males predominated among both antenatally and neonatally detected fetal VUR cases (Table 2). Bilateral dilating VUR was observed in 16 of the 30 neonatally detected cases (53%) versus in only 6 of the 21 antenatally detected cases (29%) (p=0.05). There was, however, no significant difference in the severity of VUR between the two groups when the side with the more severe grade of VUR was taken into account (p=0.16). Nor was any significant difference present in the frequency of bilateral VUR between males (24 of 36) and females (11 of 15) (p=0.24).

Table 2. Demographic features of 51 patients with fetal VUR.

	Total	Antenatal group	Postnatal group
	N (%)	N (%)	N (%)
	51 (100)	21 (41)	30 (59)
Refluxing units	86 (100)	35 (41)	51 (59)
Males	36 (71)	13 (62)	23 (77)
Females	15 (29)	8 (38)	7 (23)
	(M/F 2.4)	(M/F 1.6)	(M/F 3.3)
Unilateral VUR	16 (31)	7 (33)	9 (30)
Bilateral VUR	35 (69)	14 (67)	21 (70)
Grade of VUR			
I	0 (0)	0 (0)	0 (0)
II	17 (20)	11 (31)	6 (12)
III	30 (35)	11 (31)	19 (37)
IV	27 (31)	7 (20)	20 (39)
V	12 (14)	6 (17)	6 (12)

VUR= vesicoureteral reflux

8.2. RECURRENT URINARY TRACT INFECTIONS (UTIs)(I, III)

The frequency of recurrent and/or breakthrough UTIs in the different study groups is presented in Table 3. No significant difference was observed in the number of patients suffering from recurrent UTIs between antenatally and postnatally detected cases in any of the study groups ($p>0.05$).

Table 3. Frequency of urinary tract infections in different study groups during follow-up.

		VUR	MDK	PUV	PUJ obstruction
No. of patients with recurrent and/or breakthrough UTIs (%)		22 (43)	0 (0)	30 (65)	2 (3)
	Antenatal	8 (38)	0 (0)	14 (61)	2 (3)
	Postnatal	14 (47)	0 (0)	16 (70)	-
No. of patients with recurrent and/or breakthrough PNs (%)		15 (29)	0 (0)	22 (48)	2 (3)
	Antenatal	6 (29)	0 (0)	12 (52)	2 (3)
	Postnatal	9 (30)	0 (0)	10 (43)	-
No. of PN episodes per patient					
	Antenatal	1.5	0	2.0	1.0
	Postnatal	1.6	0	1.8	-

VUR=vesicoureteral reflux, MDK=multicystic kidney, PUV=posterior urethral valves, PUJ=pelviureteric junction, UTI=urinary tract infection, PN=pyelonephritis,

8.3. RENAL PARENCHYMAL DAMAGE (I, II, III)

Of 51 cases with fetal VUR, renal scarring was observed in the DMSA scans in 9 renal units initially. In 5 of the 51 cases (10%), scars were indicative of congenital dysplasia (split isotope uptake of less than 30% and global increased/heterogeneous echogenicity in US); in 3 antenatal cases and in 2 neonatal cases (Table 4). Two additional antenatally detected male patients with bilateral grade 5 VUR showed bilateral renal increased global echogenicity on US. In 4 neonatally detected cases, scars were of focal appearance. By the end of follow-up, new defects, all of focal appearance, had been observed in 12 additional renal units (24%) in the neonatal group, whereas no units in the antenatal group had focal renal isotope defects, either initially or at the end of follow-up ($p<0.005$). All focal scars were associated with dilating VUR, while congenital renal dysplasia was associated with grade II to V VUR. The number of total and new focal scars was significantly higher in grades IV and V VUR than in grades II and III ($p<0.05$). The new focal scars were detected at a median age of 1.8 (range 0.5 to 4.6) years. Eleven of the 12 new scars were associated with one or more episodes of breakthrough PN.

In all 48 cases with MDK, the multicystic conglomerate was nonfunctioning, with no isotope uptake (<5% of total function) in the initial DMSA scan.

Thirteen of the 46 patients with PUV (28%) were observed to have congenital renal dysplasia (<10% of total function) in the initial renal isotope scan. At the end of follow-up, acquired progressive renal scarring was observed in 11 additional renal units. Renal damage was significantly associated with the presence of VUR; parenchymal damage was observed in 17 of the 47 refluxing units (36%) versus 7 of the 45 nonrefluxing units (16%) ($p<0.05$).

Table 4. DMSA isotope scan findings: A) split isotope uptake findings in 51 patients with fetal VUR, and B) focal renal scar findings in 86 renal units with fetal VUR.

A	**Antenatal group N (%)**		**Postnatal group N (%)**	
	Initially	End of follow-up	Initially	End of follow-up
Normal split isotope uptake (≥44%)	16/21 (76)	16/21 (76)	25/30 (83)	24/30 (80)
Mild decrease in split isotope uptake (30-44%)	2/21 (10)	2/21 (10)	3/30 (10)	4/30 (13)
Overall split isotope uptake <30%	3/21 (14)	3/21 (14)	2/30 (7)	2/30 (7)

B		**Antenatal group N (%)**		**Postnatal group N (%)**	
		Initially	End of follow-up	Initially	End of follow-up
Focal scars/ renal units		0/35 (0)	0/35 (0)	4/51 (8)	16/51 (31)
Grade	I	0/0 (0)	0/0 (0)	0/0 (0)	0/0 (0)
	II	0/11 (0)	0/11 (0)	0/6 (0)	0/6 (0)
	III	0/11 (0)	0/11 (0)	1/19 (5)	4/19 (21)
	IV	0/7 (0)	0/7 (0)	3/20 (15)	10/20 (50)
	V	0/6 (0)	0/6 (0)	0/6 (0)	2/6 (33)

DMSA= renal scanning using ^{99m}technetium-dimercaptosuccinic acid, VUR=vesicoureteral reflux

8.4. RESOLUTION OF FETAL VUR DURING FOLLOW-UP (unpublished)

Among the 27 patients with fetal VUR who were treated conservatively until the end of follow-up, a high and equally good resolution rate in grades II and III reflux (35 of 37 renal units, 95%) was observed, whereas in grades IV and V, VUR ceased in only 7 of 13

renal units (54%) ($p<0.005$) (Table 5). However, even in grades IV and V VUR, a distinct tendency towards spontaneous improvement was observed during follow-up. Median age at cessation of VUR was 1.2 (range 0.3 to 6.4) years.

Table 5. Outcome of VUR in 86 refluxing renal units of 51 patients with fetal VUR.

VUR grade	Total N of renal units	Surgically treated	Conservatively followed			
			Total	Resolved	Improved	Unchanged
		N (%)	N (%)	N (%)	N (%)	N (%)
I	-		-	-	-	-
II	17	3 (18)	14 (82)	12 (86)	1 (7)	1 (7)
III	30	7 (23)	23 (77)	23 (100)	-	-
IV	27	16 (59)	11 (41)	6 (55)	4 (36)	1 (9)
V	12	10 (83)	2 (17)	1 (50)	1 (50)	-
Total N (%)	86	36 (42)	50 (58)	42 (84)	6 (12)	2 (4)

VUR=vesicoureteral reflux

8.5. OUTCOME OF MDK (II)

Complete involution of the multicystic conglomerate was observed in US in 13 of the 48 cases (27%). In 12 of these 13, involution occurred within 24 months and in one case at the age of 51 (median 14) months. Of the 32 cases to eventually undergo surgery, reduction in

the size of the cysts was observed in 19 (59%) and in 13 (41%) either no change (8) or a considerable increase (5) in the size of the conglomerate occurred during follow-up. Among the totally involuted cases, the size of the affected kidney was significantly smaller at birth than in nephrectomized cases (mean 4.6 cm vs. 5.9 cm; p=0.02) (Figure 1). The difference in size between involuted cases and those eventually undergoing surgery continued to increase during follow-up (repeat ANOVA; p<0.0001), the mean involution rate being 2.5 cm/year and 0.6 cm/year (between 0 and 18 months), respectively (p<0.0001). From 18 months onwards, no significant involution was observed in cases eventually subjected to nephrectomy (p>0.05).

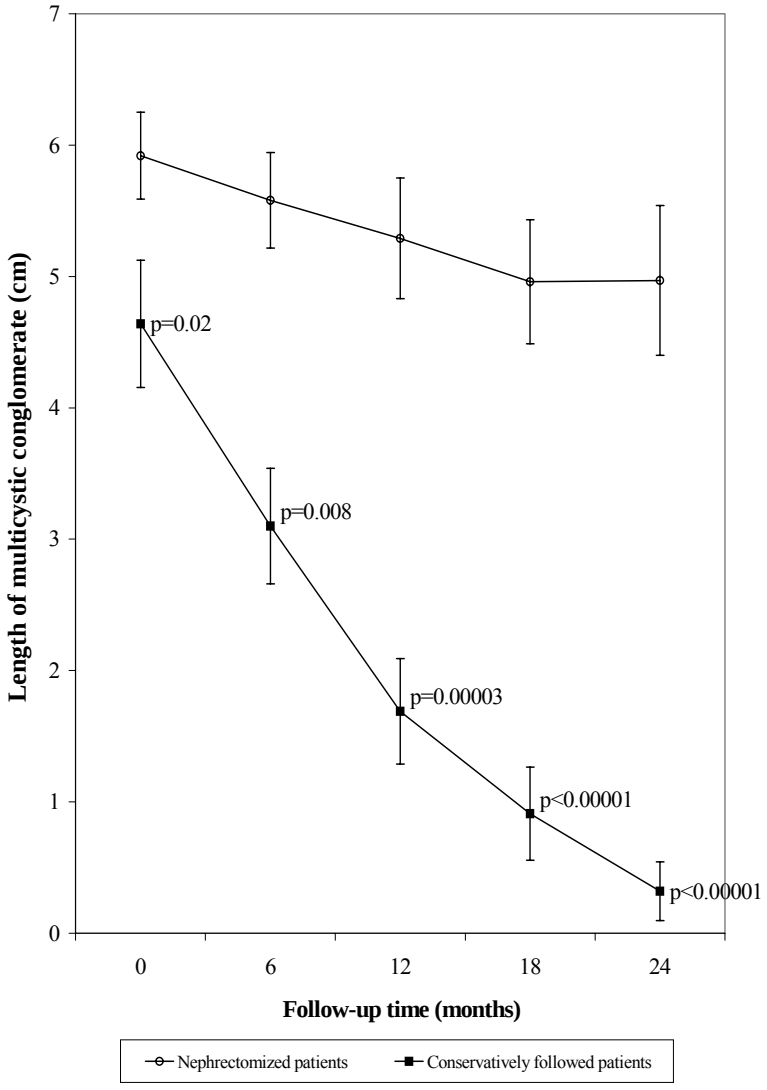

Figure 1. Difference in the mean size (±SEM) of the multicystic conglomerate among conservatively followed patients and those subjected to nephrectomy.

8.6. LONG-TERM RENAL OUTCOME OF PATIENTS WITH PUV (III)

Long-term renal outcome was poor in 14 (30%) of the 46 patients with PUV. Six of the boys (13%) developed CRF and 8 (17%) had ESRD (Figure 2). Six of the 8 patients with ESRD received transplants, and the other 2 cases are on dialysis (hemodialysis 1, peritoneal 1). Of the 32 patients classified as having a favorable long-term renal outcome, GFR was normal in 24 and moderately impaired in 8 at the end of follow-up.

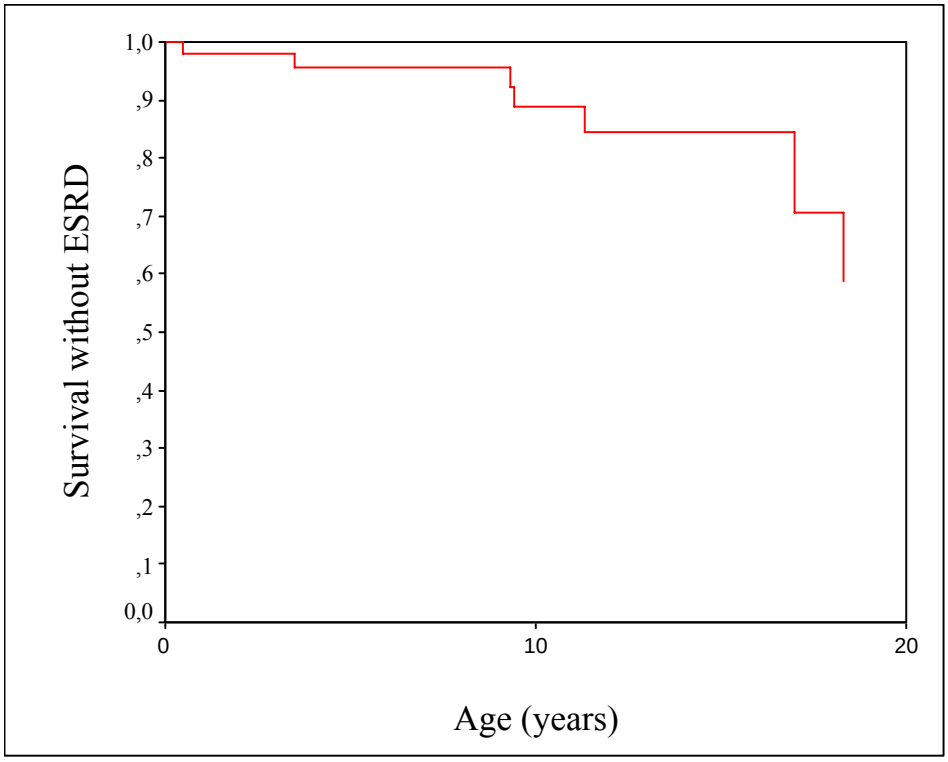

Figure 2. Rate of development of end-stage renal disease (ESRD) in 46 boys with posterior urethral valves.

8.7. PREDICTIVE FACTORS IN PATIENTS WITH PUV (III)

Nine of the 14 boys (64%) with poor renal outcome had bilateral VUR as compared with 6 of the 32 with favorable outcome (19%) ($p<0.005$). However, patients with unilateral VUR did not have significantly better outcome than those with bilateral VUR; 5 of the 17 boys (29%) with unilateral VUR vs. 9 of the 15 (60%) with bilateral VUR had poor renal outcome ($p=0.07$). Furthermore, no significant difference was present in long-term

outcome between patients with high-grade (III-V) and those with low-grade (I, II) VUR ($p=0.08$).

Patients without breakthrough UTIs had a better outcome than those suffering from repeat UTI episodes ($p<0.05$).

Nadir serum creatinine concentration during the first year of life was significantly lower in patients with a favorable outcome (mean 47±22 μmol/l) than in those ending poorly (mean 136±77 μmol/l) (Table 6; $p<0.001$). Furthermore, the initial serum creatinine levels after valve ablation or 3 days after catheter treatment were significantly higher among boys with poor outcome than in cases with favorable outcome ($p<0.005$).

Table 6. Creatinine values in 32 cases with favorable outcome and in 14 cases with poor long-term renal outcome.

	Cases with favorable outcome	Cases with poor outcome
Initial serum creatinine value		
Mean ± SD	101 ± 79 μmol/l	226 ± 116 μmol/l
Range	32-395 μmol/l	95-472 μmol/l
Serum creatinine value after valve ablation		
Mean ± SD	47 ± 22 μmol/l	184 ± 131 μmol/l
Range	29-126 μmol/l	43-523 μmol/l
Nadir serum creatinine value		
Mean ± SD	47 ± 22 μmol/l	136 ± 77 μmol/l
Range	30-126 μmol/l	43-253 μmol/l

Seventeen of the 46 boys (37%) achieved complete urinary continence by the age of 5 years. Twenty-two of 27 (81%) with a follow-up period exceeding 10 years were

continent. The mean age at the time of attaining continence was 5.0 years. No association was found between early continence (<5 years) and long-term renal outcome (p=0.11).

8.8. ROLE OF ANTENATAL DETECTION (I, III)

In the group of patients with fetal VUR, the risk of acquired renal scarring was particularly high when dilating VUR was not detected until neonatally after the first UTI. Acquired focal renal scars developed during follow-up in 19% of renal units and were observed in neonatally detected cases only (p<0.005).

Comparing patients with antenatally detected PUV with those with postnatally detected symptomatic PUV, no difference was found in the long-term renal outcome. Eight of the 23 antenatally detected cases (35%) developed poor renal function (CRF 4, ESRD 4) as compared with 6 of the 23 detected postnatally (26%) (CRF 2, ESRD 4) (p=0.21). Neither was there any difference present in the mean age of advancing to ESRD between the two groups, 9.8 ± 9.1 years vs. 11.8 ± 3.6 years (p=0.81). VUR was present to a similar extent in the two groups; 8 antenatally detected and 9 postnatally detected cases had unilateral VUR, and 6 and 9 had bilateral VUR, respectively. Fourteen antenatal patients (61%) developed breakthrough UTIs compared with 17 postnatal patients (74%) (p=0.16). No difference was observed in the number of patients with either congenital primary or acquired dysplasia (6 antenatal and 7 postnatal patients) or acquired progressive renal scarring (6 antenatal and 5 postnatal renal units). Nor was any significant difference present in initial or nadir mean serum creatinine values between the antenatal and postnatal patients (p>0.05). Eleven antenatal and 6 postnatal patients had achieved urinary continence by the age of 5 years (p=0.08). The mean age at achieving continence was 4.1 years among antenatally detected patients and 6.1 years among postnatal patients (p=0.17).

8.9. OUTCOME OF PATIENTS WITH UNILATERAL PUJ OBSTRUCTION (IV)

Of the 22 patients treated conservatively, the grade of hydronephrosis increased during follow-up in 2, remained stable in 9, improved in 3, and resolved completely in 8 (Figure 3a). Ipsilateral renal function remained good in all cases (Figure 3b). Mean split function was 51% both initially (range 43-67%) and at the end of follow-up (range 45-60%) (p=0.94).

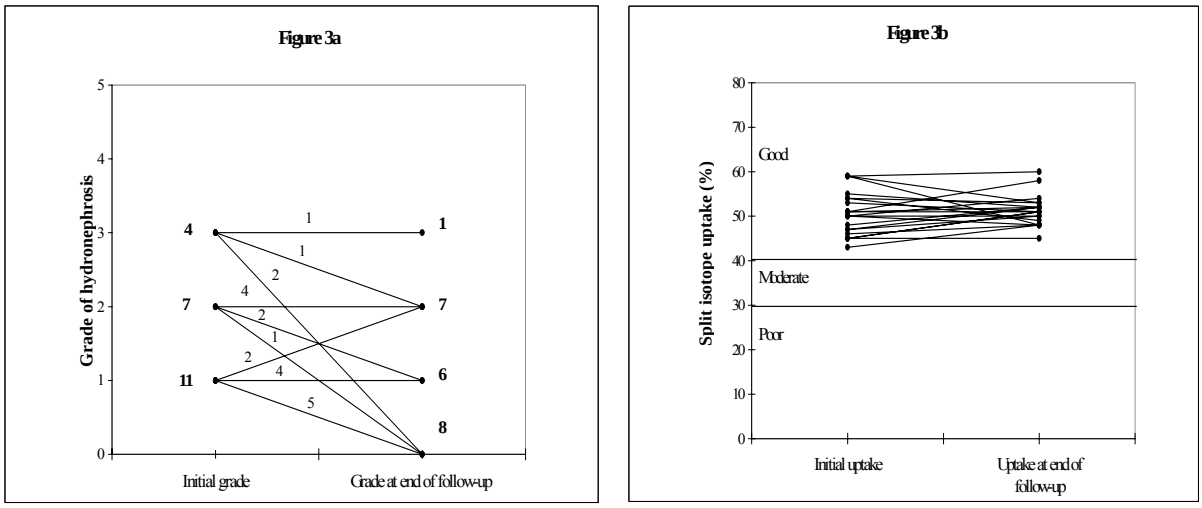

Figure 3. a) Grade of hydronephrosis and b) split renal isotope uptake in 22 patients with unilateral pelviureteric junction obstruction treated conservatively.

In 20 patients undergoing early pyeloplasty, hydronephrosis grade remained unchanged postoperatively in 2, improved in 17, and resolved completely in only one (Figure 4a). Renal function was initially good in 13 and remained unchanged after pyeloplasty (Figure 4b). Renal function was moderate in 5 cases initially, improving from moderate to good in 2, and remaining unchanged after surgery in 3. In 2 cases with initially poor function, no improvement occurred after pyeloplasty. In the entire early-operated group, the change in split renal function was insignificant after pyeloplasty (mean 43% vs. 45%, p=0.37).

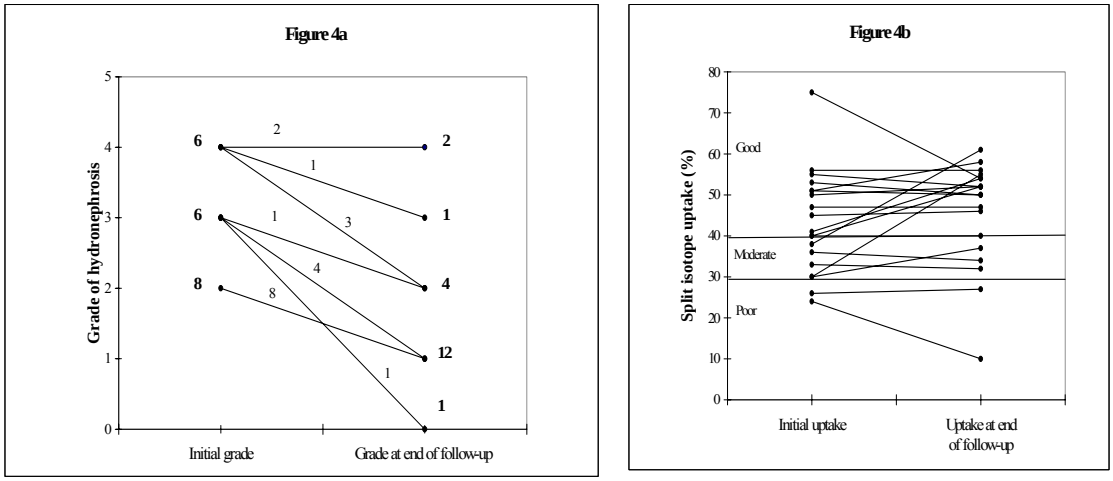

Figure 4. a) Grade of hydronephrosis and b) split renal isotope uptake in 20 patients with unilateral pelviureteric junction obstruction who were operated on early.

In 11 patients operated on later, hydronephrosis increased preoperatively in one and remained unchanged in the others. Postoperatively, hydronephrosis remained unchanged in 4 cases and improved in 7 (Figure 5a). Renal function was primarily good in 9 patients (Figure 5b). During follow-up a decline from good to moderate occurred in 3 of the 9 cases. However, moderate renal function improved to good in 2 of these 3 cases after pyeloplasty. In all 6 patients with good split isotope uptake at pyeloplasty, renal function remained stable during follow-up. In 2 cases with poor function initially, no improvement occurred either during the preoperative period or after late pyeloplasty. The mean split isotope uptake dropped from 48% initially to 42% before surgery ($p<0.05$). After surgery, the mean isotope uptake improved to 44%, representing no significant permanent loss of function ($p=0.08$).

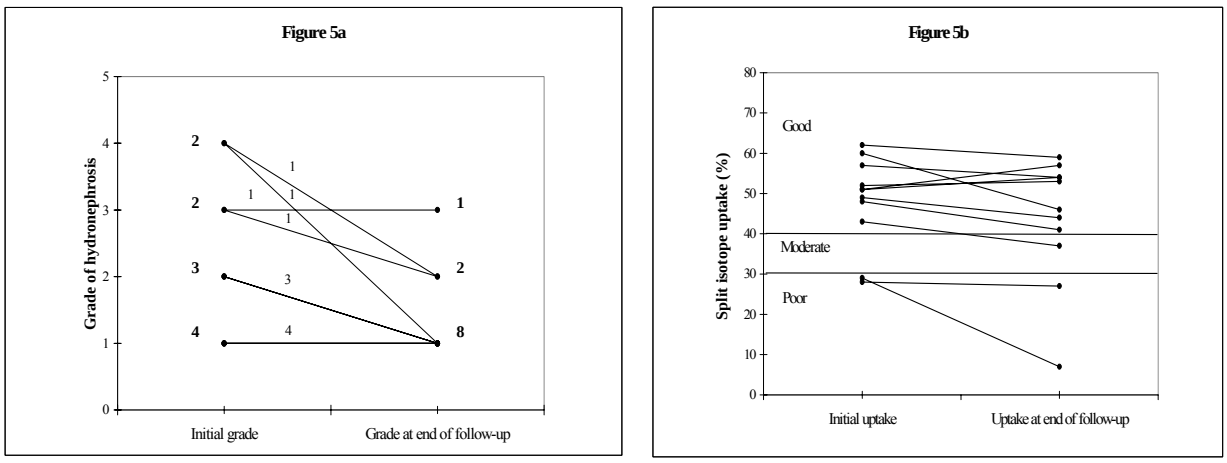

Figure 5. a) Grade of hydronephrosis and b) split renal isotope uptake in 11 patients with unilateral pelviureteric junction obstruction who were operated on during follow-up.

The grade of hydronephrosis in patients with unilateral obstruction correlated poorly with split isotope uptake in the renal scan (r=-0.2, p=0.20; Figure 6).

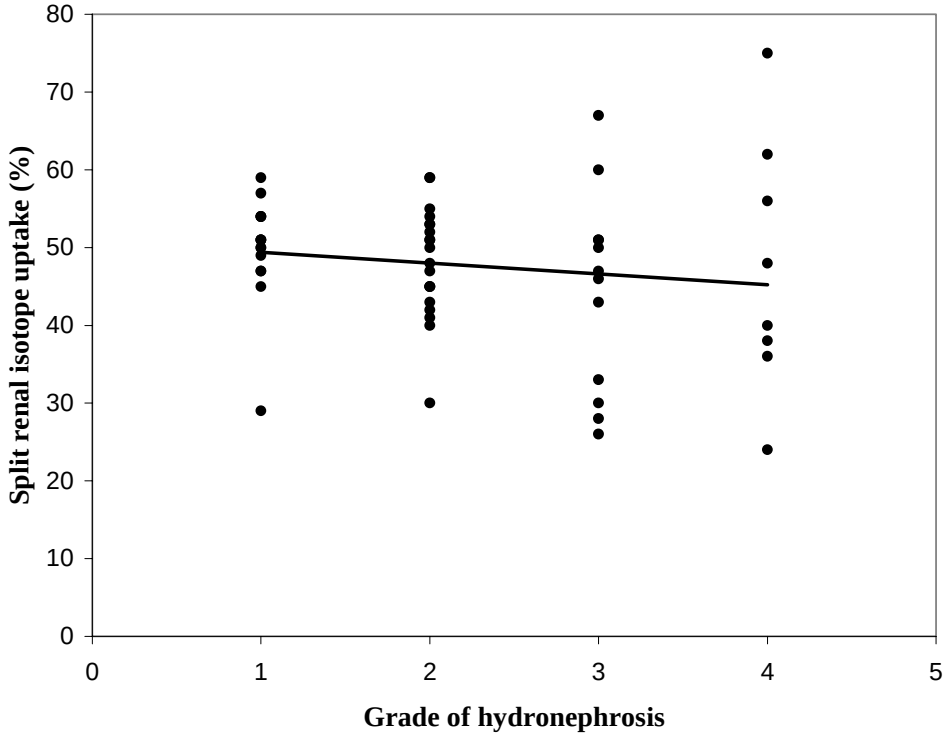

Figure 6. Correlation between grade of hydronephrosis and split renal isotope uptake in 54 patients with unilateral pelviureteric junction obstruction. Grade 1: 49.7 ± 4.1%; Grade 2: 48.2 ± 7.1%; Grade 3: 44.3 ± 12.9%; Grade 4: 47.4 ± 16.3%.

8.10. OUTCOME OF PATIENTS WITH BILATERAL PUJ OBSTRUCTION (IV)

Among cases with bilateral obstruction treated conservatively, hydronephrosis remained unchanged in 13 units, improved in one, and resolved completely in 4. Among the surgical cases, hydronephrosis remained unchanged in 3 and improved in 6. In addition, one patient with good bilateral function underwent unilateral late pyeloplasty due to an increased hydronephrosis grade from 1 to 3. After the operation, hydronephrosis improved to grade 2. In 8 patients treated conservatively until the end of follow-up, renal isotope uptake was bilaterally good initially as well as during and at the end of follow-up. In 3 of the 5

surgical patients, early renal function was good bilaterally both initially and after surgery, one of the patients undergoing pyeloplasty on one side only. In one patient with initially good function on one side and poor on the other, renal function improved after surgery. In one patient with bilaterally poor function, renal function recovered on one side and after temporary diversion remained poor on the other. Bilateral pyeloplasty at the age of 2.3 years had no effect on renal function on either side. However, at the end of follow-up, the glomerular filtration rate of all patients was normal.

9. DISCUSSION

Antenatal US offers the opportunity for early recognition and treatment of congenital urinary tract anomalies and possible preservation of renal function. Theoretically, early recognition allows surgical treatment and/or antimicrobial prophylaxis to be initiated before any further damage or complications, e.g. urinary tract infection, occur. Antenatal US was thus initially enthusiastically proposed to be of particular benefit in cases with potential mortality, such as PUV. Over the years, however, the benefit of antenatal diagnosis has been questioned. Reports on the long-term renal outcome of antenatally detected urinary tract anomalies are limited. Furthermore, in only a few studies has the long-term renal outcome of patients with antenatally detected urinary tract anomaly been compared with that of postnatally diagnosed, usually symptomatic patients.

9.1. OUTCOME OF PATIENTS WITH VUR DETECTED EITHER ANTENATALLY OR DURING THE NEONATAL PERIOD

In our study, antenatal US examination had been interpreted as normal in all cases with neonatally detected symptomatic VUR despite many of the patients having bilateral dilating reflux. Moreover, in several earlier studies, the sensitivity of US in detecting VUR has been found to be poor (Zerin et al. 1993, Tibballs and De Bruyn 1996, Farhat et al. 2000). In 4% to 28% of cases, antenatally detected hydronephrosis has been reported to be due to VUR (Najmaldin et al. 1990, Ring et al. 1993, Gunn et al. 1995, Anderson et al. 1997, McIlroy et al. 2000, Brophy et al. 2002). Consequently, all antenatally detected hydronephrosis cases are today recommended to undergo a VCUG study after birth, especially when hydronephrosis has also been detected postnatally (Woodward and Frank 2002, Phan et al. 2003).

The reported renal outcome of patients with antenatally detected VUR is controversial. Some authors suggest the outcome to be distinctly worse than when VUR is detected later, in childhood (Anderson and Rickwood 1991, Assael et al. 1998, Polito et al. 2000a).

Others, by contrast, claim fetal VUR to be a relatively benign condition (Crabbe et al. 1992, Yeung et al. 1997). With regard to demographic features, general agreement exists only on the marked preponderance of antenatally detected VUR in boys. Among our patients with fetal VUR, reflux was less common in boys (M/F 2.4) than reported generally (M/F 5 to 10), which may partly be explained by our exclusion of patients with other ureteral pathology. In earlier studies, patients with fetal VUR have been reported to present with bilateral and/or dilating VUR in about one-half of the cases (Gordon et al. 1990, Ring et al. 1993, Yeung et al. 1997, Assael et al. 1998, Herndon et al. 1999, McIlroy et al. 2000). Interestingly, we found 53% of the patients with symptomatic disease detected neonatally to also have bilateral dilating VUR, whereas this was the case in only 29% of the antenatal group ($p=0.05$). However, the frequency distribution of the different grades among our antenatal group may more accurately reflect the true demography of fetal VUR.

Renal scarring can result from either an acquired mechanism characterized by focal scarring due to UTI-associated VUR or congenital damage seen in patients with fetal VUR which is a significant element of dysplastic development. The etiology of the congenital renal damage observed in patients with fetal VUR is uncertain, but it has been postulated that sterile reflux during gestation can cause renal damage by interfering with normal renal development (metanephric differentiation) or that renal dysplasia and VUR are separate expressions of a malformed urinary tract, frequently coexisting but not necessarily causally related (Mackie and Stephens 1975). Congenital renal damage of varying severity, characterized by an overall decrease in split renal isotope uptake in the DMSA scan, has been reported to present in up to 30% to 40% of patients with fetal VUR. The criterium for decreased split isotope uptake has, however, varied from 25% to 45% in different studies. In addition, some of the previous subject pools have consisted of only patients with high-grade VUR (Ring et al. 1993, Marra et al. 1994, Assael et al. 1998, Sweeney et al. 2001). Only 14% of our patients had severely damaged kidneys (split isotope uptake in the DMSA scan of less than 30% most probably attributable to congenital renal dysplasia), which is in accordance with other earlier reports (Farhat et al. 2000, Polito et al. 2000a).

Infants with gross VUR and age <one year have been found to be at the greatest risk of further damage, particularly if PN occurs (Berg and Johansson 1983, Gleeson and Gordon 1991, Martinell et al. 1995). Consequently, patients with VUR detected either antenatally

or during the neonatal period seem to be especially vulnerable to renal damage owing to their young age and VUR often being bilateral and of high grade. Theoretically, antenatal detection with antimicrobial prophylaxis initiated directly after birth prevents most UTIs. It is therefore commonly assumed that the early administration of antimicrobial prophylaxis prevents further renal scarring in VUR. Acquired scarring has, however, been reported to occur in 0% to 60% of kidneys in fetal VUR cases, regardless of adequate antimicrobial treatment (Winberg et al. 1974, Anderson and Rickwood 1991, Yu et al. 1997, McIlroy et al. 2000). Among our patients, acquired focal renal scars developed in 19% of renal units during follow-up, explicitly in dilating VUR and only in neonatally detected cases ($p<0.005$) despite the equal frequency of breakthrough UTIs in both groups. Our results suggest that proper prophylactic medication may protect the kidney from further damage when instituted before the development of UTI. The "first hit" caused by the primary pyelonephritic episode in neonatally detected patients may be the most important cause of renal scarring becoming evident during follow-up and may also render the kidney more susceptible to development of new focal scars. To prove the benefit of antimicrobial therapy in antenatally detected cases, prospective, randomized, and placebo-controlled trials are needed. These would, however, be unethical in a neonatal population.

Because of the high spontaneous resolution rate of VUR, antimicrobial prophylaxis has been recommended as a primary mode of treatment in most studies. In our patients who were treated conservatively until the end of follow-up, the tendency for spontaneous resolution of grades II and III VUR was as high as 95%. The cessation rate of grades IV and V VUR was lower, 54%, in agreement with several reports (Yeung et al. 1997, Assael et al. 1998, Farhat et al. 2000). It should be noted, however, that 46% of our patients underwent surgical correction of VUR during follow-up for different indications. Thus, specifying the true percentages of spontaneous resolution of VUR was impossible.

9.2. OUTCOME OF PATIENTS WITH MDK

Historically, nephrectomy has been regarded as the treatment of choice in cases with MDK. At present, MDK is mostly treated conservatively by following patients with serial

US. During conservative follow-up, some multicystic conglomerates increase, some will remain unchanged, some decrease, and some involute completely. A significant number of MDKs have been reported to undergo spontaneous involution over time, the prevalence ranging from 10% at a mean of 33.5 months up to 75% at a mean of 16 months of observation (Vinocur et al. 1988, Orejas et al. 1992, Strife et al. 1993, Wacksman and Phipps 1993, Sukthankar and Watson 2000, Oliveira et al. 2001). When following MDK conservatively, many centers are content with a completely involuted MDK. It is, however, more complex if MDK persists in the US examination after an extended period of follow-up. Some surgeons follow MDK conservatively regardless of whether the size of MDK increases, remains unchanged, or decreases. In part of the centres, however, nephrectomy is still an option in treating MDK, especially in the absence of involution (Sapin et al. 1994, Webb et al. 1997, Kessler et al. 1998). We aimed at following MDK cases primarily expectantly and decided upon nephrectomy after a minimum follow-up period of 18 months. During follow-up the indication for nephrectomy was an ultrasonographically distinguishable persisting tissue mass, whether increased, unchanged, or decreased in size. Consequently, 32 of the total of 48 patients (67%) were eventually subjected to surgery, the median age at nephrectomy being 25 months. Complete ultrasonographic involution occurred in 13 of the 48 cases (27%); the median involution time was 14 months. When comparing involuted cases with surgical cases, we observed distinct differences in the clinical behavior of the multicystic conglomerate. The size of the affected kidney in involuted cases was significantly smaller at the time of birth than in nephrectomized cases. Furthermore, over an 18-month follow-up, a consistent and significantly increasing difference was present in the involution rate between the completely involuted cases and those subjected to surgery. After 18 months of follow-up, no significant reduction was observed in the size of the conglomerate in the majority of cases eventually subjected to nephrectomy, the mean involution rate being in fact -0.01 cm/year between 18 and 24 months ($p>0.05$). Based on these results, we recommend an age of about 2 years if the surgical route is chosen.

When pondering the grounds for nephrectomy, the risk of late complications must be considered. Malignant change and hypertension are potential late complications of MDK (Homsy et al. 1997, Husmann 1998, Snodgrass 2000). Eighteen cases of renal malignancy associated with MDK have been reported so far, including 11 cases of Wilms' tumor in

pediatric patients, with the remainder displaying mostly adult-type renal adenocarcinoma (Perez et al. 1998, Mingin et al. 2000). Because of the limited number of reported cases, the risk should not be overestimated. However, it should be noted that even in cases where US shows total involution of the multicystic conglomerate, some renal tissue may remain. This has been well documented in some earlier studies, where histological examination showed the presence of significant renal tissue with glomeruli, tubules, and multicystic pathology despite no residual renal or cystic tissue being observed in US (Pedicelli et al. 1986, Gough et al. 1995). Nevertheless, in our opinion, it is logical to assume that the more dysplastic tissue present, the higher the risk of later malignant change.

There have been 19 reported cases of hypertension associated with MDK (Husmann 1998, Snodgrass 2000, Oliveira et al. 2001). However, in only 7 of the 18 cases subjected to nephrectomy was hypertension resolved. The true prevalence of MDK-associated hypertension is as yet obscure, but indisputedly it is a rare occurrence. Furthermore, the true etiology of hypertension in cases with MDK is unclear, although in many of the previously reported cases, hypertension was concluded to be due to anomalies of the contralateral kidney (Husmann 1998). Pain and UTI have also been reported as late complications of MDK (Ambrose et al. 1982). The decribed cases, have, however, practically all been anecdotal.

In treating patients with MDK, the economic and psychosocial consequences should also be considered. From the economic point of view, the costs of conservative treatment should be weighed against those of surgical removal of the multicystic conglomerate. If, for example, US is carried out 6 times during the first 2 years and thereafter annually for 8 years to follow possible involution of the mass, or if US is performed every 3 months for 3.5 years to exclude Wilms' tumor, as has been proposed by Perez et al. (1998), the costs of both options at our institution exceed those of nephrectomy performed at 25 months of age. From a psychosocial point of view, the burden of prolonged follow-up on the family should be taken into account. According to the recommendations of the Multicystic Kidney Registry, the follow-up of patients with conservatively treated MDK should be life-long, including active follow-up with US every 3 to 6 months the first year, every 6 to 12 months the next 5 years, and annually thereafter (Wacksman and Phipps 1993). The time and expense of repeated outpatient visits and ultrasonography examinations, and the

family's concern and uncertainty about the child's future health undoubtedly speak against an extended conservative follow-up. Moreover, the surgical treatment alternative of MDK is relatively safe and carries only a minimal risk of morbidity (Elder et al. 1995, Homsy et al. 1997).

Regardless of whether MDK is treated conservatively or surgically, the overall outcome of these patients is favorable. The occurrence of late complications is rare. We observed one case of Wilms' tumor *in situ* but no cases of hypertension or proteinuria. Furthermore, none of our patients suffered from breakthrough UTIs. One patient did experience abdominal pain on the ipsilateral side of the MDK, and a nephrectomy was performed due to pain and the unchanged size of the conglomerate. Because the ipsilateral kidney is nonfunctioning, the prognosis of patients with MDK depends on the contralateral kidney. Associated contralateral genitourinary anomalies are common, the prevalence rate varying from 22% to 53% (Greene et al. 1971, Sapin et al. 1994, Kessler et al. 1998, Perez et al. 1998, Rudnik-Schöneborn et al. 1998). Renal function has been found to be slightly impaired in at least a portion of the patients with MDK, and therefore all patients with MDK are recommended to have long-term nephrourological follow-up (Rudnik-Schöneborn et al. 1998, Kuwertz-Broeking et al. 2004).

9.3. OUTCOME OF PATIENTS WITH ANTENATALLY DETECTED PUV

The long-term renal outcome of patients with PUV was observed to be poor in 14 of the 46 boys (30%) followed for a mean period of 12.5 years. Of the urinary tract anomalies, PUV is, however, one of the most common causes for CRF and ESRD (Smith and Duckett 1996). In earlier studies, the frequency of patients having either CRF or ESRD at the end of follow-up has varied from 22% to 68% (Warshaw et al. 1985, Tejani et al. 1986, Reinberg et al. 1992, Jee et al. 1993a, Hutton et al. 1994, Smith et al. 1996, Lal et al. 1999, Lopez Pereira 2003). Still in only a few of the previous studies has the mean follow-up time exceeded 10 years (Tejani et al. 1986, Smith et al. 1996, Lal et al. 1999, Lopez Pereira et al. 2003). The length of the follow-up has an impact on the prevalence of a poor outcome, although in part of the cases with PUV, renal function does not deteriorate before

adolescence. In addition, the lack of a uniform definition of CRF in children has an impact on results. While CRF is generally defined as a permanent reduction of the GFR, the level of GFR below which patients are considered to have CRF ranges in different centers from 9 to 80 ml/min/1.73m^2 (Tejani et al. 1986, Parkhouse et al. 1988, Dinneen et al. 1993, Proesmans 1997, Wassner and Baum 1999, National Kidney Foundation 2002, Lopez Pereira et al. 2003). Moreover, in many of the earlier studies on the outcome of PUV patients serum creatinine value alone has been used to define CRF, the definition varying from a cut-off point of 106 μmol/l (1.2 mg/dl) to CRF being 2 SD higher than normal for age (Parkhouse et al. 1988, Reinberg et al. 1992, Dinneen et al. 1993, Hutton et al. 1997, Drozdz et al. 1998). In statistical analysis, the division of patients into only two outcome groups may oversimplify matters, especially if follow-up time of the patients inside a study group varies considerably, as those followed for a shorter period may still have a progressive course. In our study, 8 of the 32 patients classified with favorable long-term outcome had moderately impaired renal function at the end of the follow-up. Thus, at least some of these cases probably progress to ESRD, especially ones with a decreased GFR before adolescence.

Different factors have been reported to have some prognostic value in the long-term outcome of individual PUV patients. Factors that have been associated with poor outcome in PUV cases are delayed diagnosis, bilateral VUR, poor detrusor function, delayed achievement of urinary continence, recurrent UTIs, and persistent elevation of serum creatinine concentration after valve ablation (Tejani et al. 1986, Parkhouse et al. 1988, Denes et al. 1997, Hutton et al. 1997). We observed poor long-term outcome to be significantly associated with the presence of bilateral VUR, breakthrough UTIs, and higher nadir serum creatinine values in the first year of life. However, no statistically significant association was found between long-term renal outcome and urinary continence or time of detection. According to different reports, the role of VUR in PUV is controversial. In some studies, neither bilateral nor unilateral VUR was observed to affect the clinical course of patients with valves (Reinberg et al. 1992, Smith et al. 1996). Consistent with our study, however, others have reported bilateral VUR to predict the eventual development of CRF and ESRD (Tejani et al. 1986, Parkhouse et al. 1988). The presence of VUR is known to predispose patients to PN. Here, also, cases with VUR suffered more breakthrough UTIs and PNs than patients without reflux. It thus follows that both of these features served as

prognostic factors of poor renal outcome in our study. The role played by early serum creatinine values in prognosis is well established, several earlier investigators emphasizing the prognostic importance of early serum creatinine levels in patients with PUV (Warshaw et al. 1985, Reinberg et al. 1992, Denes et al. 1997). The impact of urinary continence on the outcome of PUV patients is, however, more complicated. Delayed urinary continence has been reported almost without exception in cases with PUV. Postobstructive bladder dysfunction is postulated to be a principal factor in the etiology of incontinence in these patients. Persistent abnormal bladder function has also been speculated to explain, at least partly, the late onset of CRF typically seen in some of these cases. Parkhouse et al. (1988) reported early-achieved continence in cases with PUV to be associated with favorable outcome. Our study, by contrast, showed no significant association between early continence (<5 years) and favorable long-term outcome.

In recent decades, the prognosis of patients with PUV has improved considerably. Antenatal detection was initially thought to improve the outcome of patients with PUV. In our study, we found no difference in long-term outcome between antenatally and postnatally detected PUV. To our knowledge, earlier studies have also failed to show that long-term outcome of boys with antenatally detected PUV is better than that of symptomatic boys with postnatally detected PUV. In fact, in one study, the outcome of patients antenatally detected was worse than the outcome of postnatally detected patients (Dinneen et al. 1993). One explanation for the above findings is that in the more obstructive, and thus, the more severe cases, hydronephrosis is more distinct already before birth, leading to the discovery of PUV in obstetric US examinations. Furthermore, of the postnatally diagnosed patients, the most obstructive cases probably are detected early in any case, whereas cases detected later are less obstructed, and therefore, more rarely end up with permanent CRF and ESRD.

9.4. OUTCOME OF PATIENTS WITH ANTENATALLY DETECTED PUJ OBSTRUCTION

PUJ obstruction is the most common cause of antenatally detected hydronephrosis. The widespread use of antenatal US has contributed to an increase in awareness and detection the condition. The clinical severity of PUJ obstruction varies, however, considerably, and the challenge is to determine which cases are significantly obstructive and require surgery, as opposed to mere anatomical variants with no implication for renal function.

At present, controversy exists about the optimal treatment for PUJ obstruction, and when surgical correction is required, about the optimal timing of pyeloplasty. Moreover, the available diagnostic methods are not capable of defining clinically significant obstruction in neonates. According to earlier studies, a change in split renal isotope uptake is probably the most valuable criterion in determining which hydronephrotic kidney will require and eventually benefit from pyeloplasty (Ulman et al. 2000).

Forty-five of our 54 patients with unilateral PUJ obstruction had good renal function initially. In all except one case, renal function remained good irrespective of the treatment mode chosen. Undoubtedly, some cases with initially good renal function are at risk of renal deterioration during follow-up. Most of our early-operated patients probably did not actually require the surgery performed. The observation that unilateral PUJ obstruction with normal split isotope uptake is mostly a benign condition that rarely requires surgery is in accord with several earlier studies (Cartwright et al. 1992, Freedman and Rickwood 1994, Ulman et al. 2000).

Five of our patients showed moderate split function initially. In 3 other cases, renal function deteriorated from good to moderate prior to surgery. In 4 of these 8 cases, renal function improved to good after surgery. Two of these 4 underwent early surgery and 2 were operated on later. Patients either with moderate renal function initially or with function deteriorating from good to moderate may benefit from surgery. In patients with moderate renal function initially, an improvement to good may, however, be due to normal renal maturation rather than to successful surgery. In cases of renal deterioration from good to moderate during follow-up, renal recovery has been observed by some authors to

occur in all cases after surgery (Koff and Campbell 1994, Palmer et al.1998, Ulman et al. 2000, Chertin et al. 2002), whereas others have reported the loss of renal function to be irreversible (Cornford and Rickwood 1998, McAleer and Kaplan 1999, Subramaniam et al. 1999).

Of our 4 patients with poor renal function at diagnosis, 2 were operated on early and 2 late. Surgery failed to improve renal function in all of them. In at least some cases, this may be due to irreversible renal damage sustained by the patients during the antenatal period. However, in some earlier studies, poor renal function has been observed to improve significantly after surgery or occasionally without any intervention (Koff and Campbell 1994, Ulman et al. 2000).

The hydronephrosis grade has been reported to correlate with split renal isotope uptake, and it has been suggested that both patients who need surgery and those who can be followed conservatively can reliably be identified by the grade of hydronephrosis, with grades 1 and 2 depicting clinically insignificant obstruction (Ulman et al. 2000, Konda et al. 2002). In our study group, however, split isotope uptake and hydronephrosis grade correlated poorly.

A portion of the patients with bilateral PUJ obstruction can be treated conservatively but need to be closely followed up during the first years of life. In our material, there were 9 patients with bilateral grade 1 to 3 hydronephrosis with equal split function. In following these cases, the GFR value according to the Schwartz formula was used to estimate whether bilateral renal function was good or had deteriorated. One patient underwent late unilateral pyeloplasty because the grade of hydronephrosis had increased. The remaining cases were followed conservatively; both hydronephrosis grade and renal function remained unchanged or improved.

9.5. FUTURE CONSIDERATIONS

Reports concerning long-term outcome of patients with antenatally detected urinary tract anomalies remain limited, as routine obstetric US screening has only become more common since the 1980s. Now sufficient time has elapsed to study the long-term outcome of these patients and to compare the outcome of antenatally vs. postnatally detected cases to clarify the actual benefits of antenatal US screening.

Increased knowledge of the long-term outcome of different urinary tract anomalies will allow patients and their guardians to be properly counselled, which may help to decrease anxiety. In addition, by elucidating the natural history and outcome of these anomalies, we may better direct investigations and treatment to those patients who actually need them. At present, because US screening has substantially increased the number of patients detected with asymptomatic urinary tract anomalies, many useless examinations are performed on patients who do not benefit from them, which increases the work load and the expenses to our healthcare system. Unnecessary examinations also increase the stress experienced by patients and their guardians. Furthermore, the best treatment for many anomalies is still controversial. Due to increased conservatism in treatment modes, the follow-up of patients has become significantly longer, with many asymptomatic patients suggested to need even life-long follow-up, forming a further drain on medical resources.

Additional research is also needed to clarify the indications for and timing of postnatal examinations on patients with antenatally detected hydronephrosis to identify patients who would receive little/no benefit from further investigations and treatment, and to determine how long patients with different anomalies need to be followed, especially if treated conservatively.

10. CONCLUSIONS

The four original studies (I-IV) in this thesis evaluate the long-term renal outcome of patients with antenatally detected VUR, MDK, PUV, or PUJ obstruction.

The main conclusions are:

1. Renal injury occurs in an appreciable number of renal units with fetal VUR. The damage may be of congenital origin or may be acquired secondary to UTI.

2. The risk of acquired renal scarring is particularly significant if dilating VUR is not detected until neonatally after the first UTI.

3. Patients with antenatally or neonatally detected MDK can usually be followed conservatively. Involution by 18 months of age can be expected to occur in approximately one-fourth of cases. In the remaining cases, no significant involution usually occurs after 18 months. If surgery is be performed, the age of about 2 years is recommended.

4. Poor long-term renal outcome among patients with PUV is associated with the presence of bilateral VUR. Nadir serum creatinine concentration during the first year of life is a valuable parameter for assessing long-term outcome. Delayed urinary continence is common but does not exert any significant effect on renal outcome.

5. The outcome of patients with antenatally detected PUV does not differ from that of symptomatic postnatally detected patients.

6. Unilateral PUJ obstruction with initially good isotope uptake is often a benign condition. Most of these cases can thus be followed conservatively. On rare occasions, however, split renal function will decrease, and pyeloplasty may become indicated. Some cases with moderately impaired renal function might benefit from

pyeloplasty performed either early or later. In patients with poor renal function, renal recovery may be minimal despite successful pyeloplasty for irreversible antenatal renal damage.

7. Some of the patients with bilateral PUJ obstruction can be followed conservatively, but need to be closely followed up during the first years of life. In assessing renal function and indications for surgery, factors such as grade of hydronephrosis and GFR should be considered in addition to split isotope uptake.

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