Objective  To assess the clinical outcome and imaging features of neonatal primary vesicoureteral reflux (VUR).

Study design  We prospectively followed 43 infants with primary VUR identified from among a cohort of 497 infants with fetal renal pelvis dilatation. Postnatal renal ultrasound (US) examinations were performed at 5 days and 1, 3, 6, 12, and 24 months of life. Voiding cystourethrography was performed in the neonatal period and repeated at 12 and 24 months when VUR was persistent. Two radioisotopic examinations, including a 99mTc-MAG3 renogram and a plasma clearance of Cr-51 EDTA, were performed in all children with high-grade reflux.

Results  The incidence of primary VUR in our study group was 9%. Among the 43 patients followed, 11 (26%) had high-grade (IV-V) VUR and 32 (74%) had low-grade VUR. Resolution of reflux occurred in 2 of 11 (18%) patients with high-grade VUR and in 29 of 32 (90.6%) patients with low-grade VUR at age 2 years ($P<.001$). At age 2 years, 91% of the low-grade refluxing kidneys were normal on US, compared with only 35% of the high-grade refluxing kidneys. Split renal function was within normal range and single-kidney GFR was significantly increased in 13 of the 17 high-grade refluxing kidneys during follow-up. Furthermore, a strong association between dysplasia on US and poor renal function outcome was found.

Conclusions  In most infants with VUR, the reflux is of low grade and resolves rapidly. In those children with high-grade VUR, spontaneous resolution is rare at age 2 years, but persistent reflux rarely impairs the maturation of renal function.

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Fetal renal pelvis dilatation is a common abnormality, observed in 4.5% of pregnancies. Nevertheless, some controversy exists in the literature regarding the definition and significance of this finding. Measurements of the anteroposterior (AP) fetal renal pelvis diameter in different studies have suggested that a threshold value of either 7 mm or 10 mm indicated the need for a full investigation of the urinary tract in early postnatal life. There are several theories that account for the visibility of the renal pelvis during pregnancy. The distention of the urinary collecting system may be a dynamic and physiologic process due to the effect of bladder filling. However, pyelectasis may be due to significant structural abnormalities, including vesicoureteral reflux (VUR), that may adversely affect renal function or cause urinary infection or sepsis. Precisely diagnosing VUR in utero is difficult, except for the rare cases presenting with intermittent renal collecting system dilatation during real-time scanning. Due to the increasing number of studies including large populations of infants, the workup of fetal renal pelvis dilatation has become better standardized. In a recent prospective study, we showed that neonatal ultrasound (US) allows identification of infants who should not undergo voiding cystourethrography (VCUG). However, ultrasonographic changes over time have not yet been well described for VUR detected after antenatal screening. The aims of this prospective cohort study were to establish the incidence of and identify the clinical evolution of primary VUR diagnosed at birth as a result of a systematic screening of fetal renal pelvis dilatation, as well as to describe in detail the characteristics of neonatal US examination. We wondered whether some sonographic signs at entry, as well as their

| AP | Anteroposterior |
| GFR | Glomerular filtration rate |
| SGRF | Single kidney glomerular filtration rate |
| US | Ultrasound |
| UTI | Urinary tract infection |
| VCUG | Voiding cystourethrography |
| VUR | Vesicoureteral reflux |
evolution during follow-up, may indicate the presence of high-grade reflux and/or the risk of unfavorable functional prognosis. Thus we needed to precisely determine the function of the refluxing kidney. The methodology used for this combines the determination of relative function and glomerular filtration rate (GFR) of each kidney separately.6

METHODS

In a previous report, we analyzed urologic data taken from a prospective study for the years 1999-2000.5 We have extended the analysis to include 2 more years, giving a total of 4 years of systematic screening for fetal renal pelvis dilatation.

Prenatal US was performed once every trimester as part of a routine evaluation of pregnancy in an unselected population. All routine antenatal US examinations that demonstrated an AP renal pelvic diameter ≥ 4 mm in the second trimester and/or ≥ 7 mm in the third trimester were considered abnormal.7

Over the 4-year screening period, 12,036 fetuses were screened by antenatal US; of these, 592 (4.9%) were found to have a renal pelvis dilatation. Among these 592 babies, 95 (16%) were excluded from the study because of incomplete postnatal data. The remaining 497 newborns were scheduled for investigation following a standardized protocol.5 Patients with primary VUR were followed prospectively with observation and antibiotic prophylaxis for at least 2 years in our Department of Uronephrology.

At birth, informed consent was obtained from the parents. A urine sample was collected and antibiotic prophylaxis using trimethoprim (2 mg/kg/day) was started immediately. Antibiotic prophylaxis was continued in all infants with VUR until reflux resolved. All febrile episodes were investigated for urinary tract infection (UTI) during follow-up.

US

All infants underwent 2 successive neonatal US examinations of the urinary tract at 5 days and 1 month of life. Renal US examinations were also performed during follow-up at 3, 6, 12, and 24 months of life. The criteria for abnormal postnatal US included pelvic AP diameter ≥ 7 mm, calyceal or ureteral dilatation, pelvic or ureteral wall thickening, absence of corticomedullary differentiation, and signs of renal dysplasia (ie, small kidney, thinned or hyperechoic cortex, and cortical cysts).8 Renal length was defined according to the criteria of Rosenbaum et al9 and expressed in terms of standard deviation score (SDS). The postnatal US examinations were performed by the same trained pediatric radiologists using adapted equipment, with high-resolution curvilinear and linear transducers with settings optimized to pediatric patients.

VCUG

All infants enrolled in the study during the years 1999-2000 were screened with a routine VCUG, at 2 weeks of life if the first neonatal US was abnormal or at 6 weeks of life regardless of the second neonatal US examination results.5 For those infants born in 2001-2002, only those with evidence of persistent abnormal postnatal US underwent VCUG at 6 weeks of life. VCUG was repeated at 12 months and again at 24 months when reflux was persistent. VUR was graded based on the International Reflux Study Committee classification system.10

Radionuclide Studies

At least 2 radioisotopic examinations, including a 99mTc-MAG3 renogram and Cr-51 EDTA plasma clearance, were performed in all children with high-grade (IV-V) VUR during the maturation process (normally occurring in...
the first 15 to 18 months of life). The first measurement was performed before the advent of any UTI at a median age of 3 months (range, 2 to 8 months), and the final measurement was performed at a median age of 24 months (range, 18 to 24 months). Split function was determined from the early phase of a 99mTc-MAG3 renogram. Overall GFR was determined on the basis of a single blood sample obtained 2 hours after the injection of Cr-51 EDTA. Single-kidney GFR was evaluated by combining the 2 foregoing parameters. The radioisotopic examinations were performed in all cases before any surgical procedure was performed.

Statistical Analysis

Categorical data are given as proportions and expressed as percentages. Continuous data are shown as mean ± standard deviation (SD) and compared using the nonparametric Mann–Whitney test. Differences between paired samples were determined using the Wilcoxon signed-rank test. A 2-sided P value < .05 was considered statistically significant. All statistical analysis was done using STATA 7.0 for Windows (Stata Corp, College Station, Tex). Ethical approval for the study was granted by the local Ethics Committee.

RESULTS

Characteristics of the Study Population

A total of 45 patients (9%) with primary VUR were identified among the 497 patients with fetal renal pelvis dilatation. This group comprised 32 males and 13 females (male:female ratio 2.4:1; P = .01). There were a total of 67 refluxing kidneys (36 left kidneys and 31 right kidneys). Of the 45 patients, 22 (49%) had bilateral VUR. The other main pathologies found among the 497 patients with fetal renal pelvis dilatation were transient mild hydronephrosis in 18% of cases, pelviureteric junction obstruction in 13% of cases, megareter in 7% of cases, and duplex kidney in 5% of cases.

Among the 45 patients with primary VUR, 2 with low-grade primary VUR (a total of 3 refluxing kidneys) born in 1999–2000 were screened with routine VCUG even though their neonatal US results were normal. These data are not included in the results presented herein. The remaining 43 patients (a total of 64 refluxing kidneys) exhibited abnormalities on at least 1 of 2 screening neonatal US examinations. High-grade (IV–V) VUR was diagnosed in 11 (26%) of these patients (a total of 17 refluxing kidneys), and low-grade (I–III) VUR was diagnosed in 32 (74%) of these patients (a total of 47 refluxing kidneys).

In 54 of 64 kidneys (84%), reflux was detected in the kidney that appeared abnormal on neonatal US. The 10 remaining refluxing kidneys (16%) were detected on the side opposite to the sonographically abnormal kidney.

Reflux Resolution

A second VCUG was performed at age 12 months in all 43 patients with neonatal primary VUR, and a third VCUG was performed at age 24 months in all 19 patients with persistent reflux. In the whole study group of 43 patients, reflux resolved spontaneously in 24 patients (56%) and 32 kidneys (50%) at the 12-month follow-up and in 31 patients (72%) and 44 kidneys (69%) at the 24-month follow-up (Figure 2). In the 11 patients with high-grade VUR, there was complete resolution of reflux in 1 (9%) patient at 12 months and 2 (18%) patients at 24 months. In terms of renal units, high-grade reflux (n = 17) resolved in 3 kidneys (18%), remained unchanged in 10 kidneys (59%) and improved in 4 kidneys (24%) at the 24-month follow-up (Figure 2).

In the 32 patients with low-grade VUR, reflux resolved in 23 patients (72%) at 12 months and in 29 patients (91%) at 24 months. In terms of renal units, low-grade VUR (n = 47) resolved in 41 kidneys (93%), improved in 1 kidney (2%), and deteriorated in 2 kidneys (5%) at the 24-month follow-up (Figure 2).

US Examination Features According to Reflux Severity

The Table compares neonatal US and VCUG findings in the whole study group of 43 patients. Only US appearance of renal dysplasia and loss of corticomedullary differentiation were strongly associated with severe forms of VUR (P = .001 and .004, respectively). In these cases, however, loss of corticomedullary differentiation was probably related to renal dysplasia. The other US abnormalities (ie, pelvic dilatation, calyceal or ureteral dilatation, and pelvic or ureteral wall thickening) found on neonatal US scan provided no useful information on the level of VUR, because they occurred with equal frequency in both high-grade and low-grade reflux (Table).

Figure 3 shows the US evolution of the refluxing kidneys according to their initial VUR grade (high-grade vs low-grade) during follow-up. All 17 kidneys with high-grade VUR were abnormal on US until age 3 months; 3 (18%) and 6 (35%) of them demonstrated complete disappearance of abnormalities on US at age 12 months and 24 months, respectively. In the 47 kidneys with low-grade VUR, neonatal US was abnormal in 37 (79%) of cases. The 10 cases (21%) with normal aspect on US were found on the side opposite to
a sonographically abnormal kidney. US findings were normal in 41 (87%) and 43 (91%) of these kidneys at age 12 and 24 months, respectively.

The frequency of echographic abnormalities was evaluated in patients with persistent VUR at age 12 months. Fourteen of the 16 kidneys (88%) with persistent high-grade VUR at age 12 months were abnormal on US. In contrast, only 6 of the 16 kidneys (38%) with persistent low-grade VUR exhibited US abnormalities at age 12 months.

**UTI**

UTI was diagnosed in 9 patients (21%), 5 with high-grade VUR and 4 with low-grade VUR. In 2 of the 5 patients with high-grade VUR, the cause of UTI was of iatrogenic origin (the first case shortly after VCUG despite chemoprophylaxis, and the second case after a surgical procedure). In 1 patient with high-grade VUR, noncompliance with antibiotic prophylaxis was proven. In the remaining 6 patients, UTI occurred despite preventive antibiotic treatment.

**Surgery**

Antireflux procedures were performed in 4 (9%) patients because of recurrent UTI. All 4 of these patients had high-grade VUR. Three patients underwent endoscopic treatment for VUR using subureteral injection of polytetrafluoroethylene (Teflon), and 1 patient underwent extravesical reimplantation, according to the surgeon’s choice.

**Renal Function in Cases With High-Grade VUR (11 Patients; 17 Refluxing Kidneys)**

In 8 patients (a total of 11 high-grade refluxing kidneys), split function was initially in the normal range and remained unchanged during follow-up (48.5% ± 2.1% and 50% ± 0.5%, respectively; P = .75). In all 8 of these patients, single-kidney GFR was initially normal and exhibited normal maturation between the first and last measurements from 30.7 ± 7 mL/min/1.73 m² to 53 ± 8 mL/min/1.73 m² (P = .001).

One patient with early severe chronic renal failure had bilateral VUR of grade V. Split function was initially 30% left and 70% right at age 3 months and became 20% and 80% at age 24 months, suggesting a significant decrease on the left side. However, overall GFR was very low at study entrance (23 mL/min/1.73 m²) and remained unchanged during follow-up. Single-kidney GFR was therefore very abnormal on both sides at the beginning (7 mL/min/1.73 m² on the left and 16 mL/min/1.73 m² on the right) and did not change significantly at age 24 months (5 and 17 mL/min/1.73 m², respectively). The significant change in split function may be due, at least in part, to the inaccuracy of the measurement at this low level of overall GFR.11

In the last 2 patients in this group, renal dysplasia was unilateral even though VUR grade was similar on both sides (grade V). Split function of the worst-functioning kidneys was initially 15% and 40% and decreased to 8% and 30%, respectively. Overall GFR was low at entrance (40 and 50 mL/min/1.73 m² at age 6 months, respectively) and remained

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Table I. Comparison between neonatal US and VCUG findings in 43 infants with primary VUR

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<tr>
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<td>Male/Female</td>
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<td>AP</td>
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For infants with bilateral VUR, only the kidney with the highest grade of reflux is recorded. D, pelvic dilatation (abnormal kidneys); AP, mean anteroposterior pelvis diameter in mm; C, calyceal dilatation, (abnormal kidneys); U, ureteral dilatation (abnormal kidneys); PUW, pelvic or ureteral wall thickening (abnormal kidneys); CMD, corticomedullary differentiation (abnormal kidneys); Dyspl, signs of dysplasia (abnormal kidneys); NA, not available.

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Figure 3. US evolution of the refluxing kidneys in relation to the initial grade of VUR (high-grade [n = 17] vs low-grade [n = 47]) during follow-up.
low at age 24 months despite a significant increase (66 and 65 mL/min/1.73 m², respectively). Single-kidney GFR was initially low on the worst side (6 and 22 mL/min/1.73 m², respectively) and remained unchanged at age 24 months (5 and 17 mL/min/1.73 m², respectively). In contrast, the contralateral kidneys showed a significant increase in single-kidney GFR (+27 and +18 mL/min/1.73 m², respectively). This significant maturation was not sufficient to maintain a normal overall GFR, however.

Figure 4 shows the individual single-kidney GFR evolution of all of these 17 high-grade refluxing kidneys. As mentioned earlier, only 4 kidneys (3 patients) with an initial low single-kidney GFR did not improve during follow-up. All of these poorly functioning kidneys were dysplastic and of small size on US compared with those kidneys with favorable evolution (-3.6 ± 2 SDS and 1.2 ± 1 SDS, respectively).

DISCUSSION

The prevalence of VUR has been estimated at 2% of the pediatric population. In children with VUR demonstrated on VCUG, there is a tendency for the grade of VUR to improve or for VUR to resolve with increasing age. However, VUR has been identified as a risk factor for the development of UTI and is present in 1/3 of young children presenting with this problem. In addition, some children with prenatal suspicion of VUR have renal lesions, including cortical cysts, before the advent of UTI. Some investigators consider these lesions as indicative of congenital dysplasia, whereas others think more in terms of acquired renal scarring, which makes the issue rather confusing. As a result, some studies have suggested that management of asymptomatic patients with antenatally diagnosed renal pelvis dilatation should be complete, to allow early identification of VUR and initiation of prophylactic treatment. This has generated a massive workload for radiology departments and has exposed large numbers of neonates to significant radiation without much evidence of benefit.

The arguments regarding the importance of diagnosing all cases of neonatal VUR center on the perceived magnitude of the risks of infection and functional decline. However, current evidence suggests that only patients with grade IV–V VUR are at high risk for serious adverse outcome and delayed resolution. In asymptomatic children with low-grade VUR, radiologic demonstration of reflux is probably of limited usefulness. The present study, in accordance with other studies, does not confirm previous findings suggesting that most infants with neonatal VUR have high-grade reflux. Such discrepancies among studies are due to the fact that over the last decade, sophisticated technology has allowed the prenatal detection of small renal pelvis dilatations, and thus more infants with primary VUR (particularly low-grade VUR) have been identified using such small threshold diameters. Moreover, because some investigators have made a case for performing VCUG in all infants presenting with antenatally detected renal pelvis dilatation irrespective of the degree of renal collecting system dilatation on postnatal US, the number of VCUGs performed has halved the number of VCUGs performed. We believe, in common with other authors, that screening with neonatal US is preferable to routine VCUG in all babies with fetal renal pelvis dilatation. Although occasional cases of VUR could have been missed by our current approach, the risk of missing low-grade reflux is outweighed by the benefit of avoiding unnecessary invasive examinations in most healthy infants. Nonetheless, parents should be advised that if their infant develops a fever of unknown origin, then the urine should be investigated for infection. This approach could result in prompt self-referral of ”missed” cases.

In our population of infants with fetal renal pelvis dilatation, despite this restrictive attitude, VUR was of low-grade in 74% of cases, with a high rate of spontaneous resolution at 24 months (Figure 2). Note that, in contrast to our own findings, the accuracy of US compared with VCUG in diagnosing VUR has been found to be disappointingly low. This is probably due to the fact that formerly reflux was diagnosed mainly in children being investigated for UTI, not in healthy neonates. The present study highlights the importance of taking into account the age at which renal US scan is performed. As a matter of fact, initial US abnormalities corresponding to low-grade reflux disappeared rapidly from the neonatal period to age 24 months (Figure 3). We believe that early renal pelvis dilatation is probably related to the highly compliant nature of the collecting system in this age group. On the other hand, US criteria of renal dysplasia and loss of corticomedullary differentiation persisted during the follow-up period and were exclusively associated with severe forms of VUR (Table). The other US criteria were not sensitive
Deteriorating renal function is the most significant adverse outcome defining renal risk when a conservative strategy is chosen. One of the objectives of the present study was to evaluate the high-grade refluxing kidneys the initial level of split function and single-kidney GFR and the further evolution of these parameters. Our data showed that split function as measured from renograms was normal in most cases and remained stable throughout follow-up. However, in cases with bilateral reflux nephropathy, a major factor limits the reliability of differential split function, because the analysis of this parameter relies on comparing isotope uptake between kidneys. As an example, 1 of our patients had bilateral reflux nephropathy, low split function on 1 side, and high split function on the contralateral side. This contrasted with low single-kidney GFR and poor functional maturation on both sides and demonstrated the contribution of an absolute measurement of single-kidney GFR.

For these high-grade refluxing kidneys, we expected to see an impaired maturation process in relation to the loss of functional parenchyma. Surprisingly, however, we observed a significant single-kidney GFR increase in 76% of cases (Figure 4). Therefore, significant maturation of the renal function occurred in these kidneys at a median age of 3 to 24 months. Only 4 kidneys, with an initial low single-kidney GFR, exhibited unfavorable improvement during follow-up (Figure 4).

In terms of comparing US findings and renal function, we found that the smallest kidneys had the poorest prognosis in terms of single-kidney GFR. These findings add to the growing body of evidence indicating that renal impairment associated with severe reflux is congenital in nature and is likely due to antenatal dysplasia.

REFERENCES