

Outcome of Vesicoureteral Reflux in Infants: Impact of Prenatal Diagnosis

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Abstract

Objective: Vesicoureteral reflux (VUR) is an important disorder that could be diagnosed in antenatal or postnatal period. The natural history of VUR seems to be different between prenatal or postnatal forms of the disease. We compared the natural history and outcome of vesicoureteral reflux in infants less than one year old diagnosed prenatally or postnatally.

Methods: All infants less than 12 months old with VUR were enrolled in two groups. Group 1 composed of patients with antenatal hydronephrosis and group2, infants with diagnosis of VUR because of UTI or other postnatal problems. We followed patients for an average of 33 months. Outcome was assessed by several factors: somatic growth, need for surgery, resolution, occurrence of UTI and scar formation.

Findings: We studied 236 renal units in 152 patients (70 boys, 82girls), 67 patients in group 1 and 85 patients in group2. Occurrence of recurrent UTI was 10.6% with no significant difference between two groups. Reflux resolved in postnatal group more significantly than in the other group (73% vs 49%). Scar developed similarly in both groups (15% vs 25% of renal units). Surgery performed in 7 (8.2%) of postnatal and 4 (6%) of prenatal group with no significant differences between the two groups.

Conclusion: VUR diagnosed prenatally has similar importance and outcome as postnatal diagnosed one. We suggest performing the same imaging and treatment procedures for prenatally and postnatally diagnosed VUR.

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Introduction

Vesicoureteral reflux (VUR) is an important disorder in children because of high association with urinary tract infection (UTI) and permanent renal damage (scar)^[1]. Reflux-associated nephropathy is one of the most important causes of end stage renal disease and kidney transplantation in children and adults^[2,3].

Currently most cases of VUR are not diagnosed until the patients presented with urinary tract infection, the condition that increases risk of renal damage.

The advent of prenatal ultrasonography has enhanced the early detection of various urinary tract abnormalities such as VUR. Reflux was detected in 15-30% of infants with abnormal prenatal ultrasound findings^[4-7].

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Controversy exists regarding the natural history and treatment of VUR diagnosed antenatally and those detected later in life, usually after urinary tract infections. Prenatal diagnosis should be an ideal opportunity to detect VUR earlier and prevent later renal damage but some authors suggested that fetal vesicoureteral reflux is essentially benign and need less aggressive investigation and management^[8,9]. Conversely others have opposite idea^[10,11]. They believe that there is no difference between two forms of VUR according to natural history and outcome.

The aim of this study was to assess the natural history and outcome of vesicoureteral reflux in infants less than 1 year and compare prenatally detected with those detected later during the first year of life.

Subjects and Methods

This prospective study was carried out in BooaliSina university hospital, Sari, IRAN, from September 2004 to March 2012. The study was approved by the Research committee of Mazandaran University of medical sciences. All parents were given written informed Consent before enrolling the infants into the study.

All infants less than 12 months old with VUR were enrolled in this study. VUR was diagnosed in the follow up process of antenatal diagnosed hydronephrosis or postnatal conditions such as urinary tract infections. Reflux was diagnosed by cystography and classified as grade one to five according to severity. All infants with any grade of reflux enrolled in study. Infants with reflux associated with any other pathological condition and those with incomplete follow up were excluded.

We divided children into two groups. Group 1 consisted of patients with antenatal hydronephrosis that VUR was detected on postnatal investigation. In group 2 there were infants that had normal prenatal ultrasound but VUR was diagnosed during the first year of life following the workups for UTI.

We followed all infants with prenatal hydronephrosis that were referred to our clinic. All infants were studied by urinary tract

ultrasonography performed at first and six weeks of age. voiding cystourethrogram (VCUG) was performed in infants who had persistent hydronephrosis on both postnatal sonographies. We ordered VCUG for children less than one year old with urinary tract infection. Reflux grade was classified at first VCUG according to the system proposed by International Reflux Study Committee.

All patients received prophylactic antibiotics until resolution of reflux or improvement to lower nondilating grades of reflux. We used cephalixin, cotrimoxazole, amoxicillin for prophylaxis. We prospectively followed patients at least for six months for assessment of defined outcomes including somatic growth, need for surgical intervention, reflux resolution, formation of scar, hypertension and ultimately episodes of UTI.

For assessment of somatic growth we considered Height for age Z score (HAZ) at 12±2 months of age.

Reflux resolution was defined based on results obtained by follow up VCUG at 12-18 months later as: no change, improvement of less than 50% in severity of VUR, improvement of more than 50% in severity and cure (normal cystography on follow up). Hypertension was defined as values persistently above the 95th percentile for age, gender and height on three consecutive visits.

Scar was defined as permanent change in renal outline demonstrated by dimercaptosuccinic acid (DMSA) scintigraphy performed at the age of six months or later in prenatal group and at least six months after infection in the other group. The Scar severity was classified as grade 1 to 4 according to international classification as follows: normal=0; focal scarring in one region=1; scarring involving two regions=2; scarring involving all three regions=3; and generalized reduction in cortical mass=4.

The number of confirmed UTI was considered as a prognostic factor. UTI was defined as growth of at least 100,000 colony forming unit/ml in urine obtained by bag, 1000 colonies in catheter sample or any colony in urine obtained by suprapubic aspiration. We considered more than two episodes of infections as recurrent UTI. Neither of specialists that performed radiographic or scintigraphic imaging was aware of the infants' data.

Data analysis was done by SPSS12 software.

Table 1: Demographic and basic clinical features of patients

	Prenatal group	Postnatal group	P-value
Number of patients	67	85	NA
Number of renal units	98	138	NA
Sex			
Male (%)	45 (67.2)	25(70.6)	<0.001
Female (%)	22 (32.8)	60(29.4)	
Length of follow up (months) [Mean (SD)]	29.17(19.04)	36.03(18.34)	0.7

NA: not applicable; SD: Standard deviation

Statistical analysis of the differences between groups was determined by χ^2 and Fisher exact test and Wilcoxon on signed-rank test. *P*-value <0.05 was considered statistically significant.

Findings

A total of 152 patients was enrolled in the study (70 boys and 82 girls). Sixty seven infants presented with antenatally detected hydro-nephrosis and 85 infants presented with UTI and other complaints after birth.

Demographic and basic clinical features of patients are presented in Table 1. As expected, most of patients of prenatal group were male, whereas the female sex was more common in postnatal group. The reflux severity was slightly higher in postnatal group (Tables 1 and 2). There were 68 patients with unilateral and 84 patients with bilateral VUR, a total of 236 refluxing renal units were included in analysis, 98 in group 1 and 138 in group 2.

The average length of follow up was 33±19 (range; 6-94) months with no significant difference between two groups.

Outcome

UTI: There were 16(10.5%) patients with recurrent UTI, four patients of group 1 and 12 infants of group 2. There was no significant

difference in the occurrence of recurrent UTI between two groups (*P*=0.1).

Renal scar: Renal scars developed in 46 (19.5%) of renal units including 25 units in group 1 and 21 units in group 2. There was no significant difference between two groups (*P*=0.3). Severity of scar developed in the two groups is shown in Table 3. Somatic growth: At approximately 1 year of age, the mean height-for-age Z score was 0.03 (±1.13) and -0.09 (±1.20) for groups 1 and 2 respectively (*P*=0.5).

Reflux Resolution: Reflux was unchanged in 7 (16.7%) and cured in 20 (49%) of renal units in group 1 patients at 12-18 months of age, these values were respectively 12 (10.3%) and 93 (73%) of renal units for group 2 (Table 4). There was a significant difference in resolution of VUR (*P*<0.001). Reflux in infants of postnatal group tends to resolve spontaneously more than that in prenatal group. The sex of patient had no significant influence on outcome of VUR (Table 5).

As predicted, higher grades of reflux were associated with less chance of spontaneous resolution of VUR. Reflux resolution in end of study for grades one to five was 80%, 82.7%, 70.6%, 60.7% and 24.2% respectively.

Surgery: Antireflux procedures were performed in 4 (6%) infants of group 1 and also 7 (8.2%) of group 2 patients, the values with no statistically significant difference (*P*=0.6). The primary indications of surgery were scar in 9 (81.8%) cases, and no improvement of higher grades VUR

Table 2: Severity of reflux in prenatal and postnatal groups

Grade of reflux	Prenatal group (%)	Postnatal group (%)	P-value
One	4(4)	2(1)	0.03
Two	20(20)	41(30)	
Three	36(37)	60(44)	
Four	14(14)	20(15)	
Five	24(25)	15(11)	

Table 3: UTI development, scar severity and reflux resolution in two sex groups

Factor	Male Number (%)	Female Number (%)	P-value
Recurrent UTI	4 (5.7)	12 (14.6)	0.07
Scar severity	Grade0	81(75)	109(85)
	Grade1	10 (9)	8(6)
	Grade2	3 (3)	5 (4)
	Grade3	8 (7)	2(2)
	Grade4	6 (6)	4(3)
Reflux resolution	Un-changed	11(14)	14(11)
	<50% improvement	8(10)	11(9)
	>50% improvement	10(13)	17(14)
	Cure	51(64)	81(66)

UTI: Urinary tract infection

after 12-24 months therapy in 2 (18.2%) other cases.

Discussion

Prenatal ultrasound has changed the detection and management of many urologic abnormalities. VUR, found in 15-30% of cases of prenatal hydronephrosis, is one of the most common abnormalities^[2,3,12,13]

Early detection and management of reflux with antenatal ultrasound could improve long term outcome^[14,15], but controversy exists regarding the natural history and management of this entity. Some authors have reported that prenatal VUR could lead to renal damage (like other forms of primary VUR) while other studies suggest that fetal VUR is relatively benign^[10,11,16,17].

In our study 152 infants with VUR were studied in two separate groups with antenatal and postnatal diagnosis. Similar to other studies, the sex predominance belonged to boys in antenatal and girls in postnatal group. This sex difference seems initially a conflicting factor but there was no significance difference between the two sexes

in terms of most prognostic factors studied.

The severity of reflux was slightly higher in postnatal group relative to antenatal group. This is not unexpected because we enrolled symptomatic infants in postnatal group. It is noteworthy that 39% of asymptomatic infants had high grade reflux. Farhat et al found these grades of VUR in 48% of patients^[9] and Upadhyay et al showed that 39% of renal units had VUR grade 4 or 5^[18]. This significantly high percentage of dilating reflux emphasizes the opinion that screening is mandatory for all neonates with history of antenatal hydronephrosis^[4].

What is the long term course of VUR? We followed our patients for an average of 33 months. VUR resolved spontaneously in 49% of our antenatal VUR patients and 73% of postnatal patients, whereas 29% and 19% of patients had no significant improvement, respectively. It is notable that overall resolution rate of prenatal VUR was significantly lower compared to postnatal VUR pointing that prenatal VUR may persist at least similar to and even more than the reflux observed in any other time of life. Ismaili et al reported that 69% of their 67 refluxing renal units resolved within 24 months^[19]. Upadhyay et al showed 52% cure and 24% persistence of VUR^[18].

In our and two other studies the severity of VUR

Table 4: Severity of scar in renal units in prenatal and postnatal groups

Scar severity	Prenatal group	Postnatal group	P. value
No scar	73 (75)	117 (85)	0.3
Grade 1	9 (9)	9 (7)	
Grade 2	5 (5)	3 (2)	
Grade 3	5 (5)	5 (4)	
Grade 4	6 (6)	4 (3)	

Table 5: Patterns of reflux resolution in two prenatal and postnatal groups

Resolution pattern	Prenatal group	Postnatal group	P. value
No change (%)	7 (11)	18 (13)	<0.001
Less than 50% resolution (%)	11 (17)	8 (6)	
More than 50% resolution (%)	16 (24)	11 (8)	
Full improvement (cure) (%)	32 (49)	100 (73)	

has direct influence on persistence of VUR. Sjostrom et al followed 115 infants with grade 3-5 reflux and reported that spontaneous resolution occurred in only 27% of their patients and 12% of them improved to grade 2 and 1 reflux^[20].

In our opinion, this persistence rate of VUR is important and we need to follow infants until complete resolution of reflux, but another important question is: What is the relation between VUR and renal damage?

Renal scar was observed without any statistical difference in 25% of antenatal VUR and 15% of postnatal VUR and near half of them were severely damaged. Farhat and coworkers detected renal scarring in 12 out of 54 renal units^[9]. In a similar study, Sjostrom and coauthors found that half of their children had generalized renal scar and one-quarter had focal damage^[20]. In study of Upadhyay et al, scar was seen in 23% of renal units prior to study but only two new scars developed in 14 patients that were followed^[18].

Near to other studies we found no case of CRF and HTN in our patients^[18,19,21]. Sjostrom wrote that from 84 refluxing infants with history of antenatal hydronephrosis, 27 had chronic kidney disease (CKD) stage 2 and three had CKD stage 3 and there was a significant difference between prenatal and postnatal group^[20]. We found no significant difference between two groups although this conclusion is not strictly appropriate in this relatively short time of follow up.

And finally, one helpful item is the frequency of urinary tract infections in both groups. Recurrent UTI was observed in only 16 infants with no significant difference between the two groups. Recurrent UTI was observed with 15-25% frequency in some mentioned studies^[9,18,19]. Surprisingly, Estrada et al reported a very low rate of UTI. UTI developed in only 1.3% of the patients who were screened and did not have VUR and, therefore, were not receiving antibiotics. Of the

screened patients with VUR who were receiving prophylactic antibiotics, UTI developed in 1.6% at a mean age of 9.4 months. In 363 patients who did not undergo an initial voiding cystourethrogram, a febrile urinary tract infection developed in 16 (4.4%) patients at a mean age of 9.3 months. They concluded that in patients with a history of prenatal hydronephrosis, identification of VUR and use of prophylactic antibiotics significantly reduces the risk of febrile UTI^[10].

Based on ours and some other reports, infection episodes were seen in a considerable rate and need attention and appropriate prophylaxis.

Our study has one limitation: we did not have baseline scintigraphic data about renal damage immediately after birth and therefore some reported scars in both groups may belong to congenital events. It was not our routine protocol to perform DMSA in first two months of life due to physiologically decreased renal function.

Conclusion

Our study confirmed that VUR diagnosed in the setting of prenatal hydronephrosis has relatively similar importance and outcome. The findings of our study emphasize the importance of early diagnosis and management of the prenatal VUR after birth.

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Conflict of Interest: None

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