

Significance of Postnatal Follow-up of Infants with Vesicoureteral Reflux Having Antenatal Hydronephrosis

Murat Kangin^{*1}, MD; Nejat Aksu^{*2}, MD; Onder Yavascan², MD; Murat Anil³, MD;
Orhan Deniz Kara⁴, MD; Alkan Bal², MD, and Fulya Kamit², MD

1. Diyarbakir National Hospital, Diyarbakir, Turkey
2. Department of Pediatric Nephrology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey
3. Department of Pediatrics, Izmir Tepecik Training and Research Hospital, Izmir, Turkey
4. Ege University, Faculty of Medicine, Department of Pediatric Nephrology, Izmir, Turkey

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Abstract

Objective: To evaluate the frequency of urinary tract infections (UTIs) and degree of renal parenchymal damage as well as the parameters of growth, development and nutritional status in antenatal hydronephrosis cases with vesicoureteral reflux (VUR).

Methods: Infants, whose antenatal ultrasonography (US) showed a fetal renal pelvic diameter of 5 mm or greater were investigated. Of the 277 infants with antenatal HN, 36 [56 renal units (RUs)] were diagnosed with VUR. All cases with VUR were evaluated in terms of the frequency of UTIs, scars appearing on ^{99m}Tc-technetium-dimercaptosuccinic acid scan (DMSA), growth and development [height and weight standard deviation scores (HSDS and WSDS)], and nutritional status [relative weight (RW)]. Statistical evaluation was performed using the Chi-squared test.

Findings: Of these 36 patients with VUR, 25 (69.4%) were males and 11 (30.6%) females. Of the 56 RUs, 48 (85.7%) had severe VUR (\geq Grade III). The mean duration of postnatal follow-up was 37.8 ± 24.50 months. The annual UTI frequency was found to be 1.25 ± 0.83 episodes/year. Of these 36 infants, 32 (88.8%) recovered from VUR following either medical (17 patients, 47.2%) or surgical (15 patients, 41.6%) treatment. The initial DMSA showed parenchymal defects in 16 (44.4%) RUs, and 4 RUs showed recovery in the final DMSA. Although statistically insignificant ($P > 0.05$), initial growth and development (HSDS: -0.17 ± 0.86 ; WSDS: 0.00 ± 0.14) and nutritional status (RW: 98.19 ± 8.81) values gradually improved (0.05 ± 1.06 , 0.06 ± 1.071 and 101.97 ± 14.85 , respectively).

Conclusion: Postnatal early diagnosis and appropriate management of VUR in infants with antenatal hydronephrosis can prevent the occurrence of frequent UTIs, renal scarring and malnutrition, enabling normal growth and development.

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* Corresponding Author;

Address: Diyarbakir Devlet Hastanesi Bashkeklik Diyarbakir, Izmir, Turkey/ Tepecik Egitim ve Arastirma Hastanesi Cocuk Sagligi ve Hastaliklari Klinikleri Izmir- Turkey

E-mail: m_kangin@hotmail.com; nejataksu@hotmail.com

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Introduction

As antenatal ultrasonography (US) has become more widely used, the number of fetal hydronephrosis diagnoses has increased. Hydronephrosis is detected in 1:100 to 1:500 of fetuses evaluated with antenatal US^[1].

Vesicoureteral reflux (VUR) is seen in 10-20% of these cases^[2]. VUR is an important risk factor in the etiology of recurrent urinary tract infections (UTIs) in childhood. Urine backflow to the collecting system due to reflux, particularly when accompanied by fever, may lead to serious health problems: hypertension and renal failure^[3], growth and development can be adversely affected by recurrent UTIs and the resultant lack of appetite, increased catabolism and tubulointerstitial lesions that develop secondary to reflux nephropathy, urinary concentration defects, electrolyte loss and acidosis^[4]. In addition, since reflux nephropathy is one of the major reasons of end stage renal failure (ESRF), it is advised that all infants with antenatal hydronephrosis be scanned for VUR^[2].

The objective of this study was to evaluate UTI frequency, degree of renal parenchymal damage and parameters of growth, development and nutritional status in antenatal hydronephrosis cases with VUR.

Subjects and Methods

Among 277 patients with antenatal hydronephrosis (AH) referred to our hospital from Izmir Ege Maternity and Gynecology Training and Research Hospital during 1998-2007, 36 infants with VUR, diagnosed postnatally, were investigated prospectively. Each kidney detected to have reflux was referred to as a "renal unit" (RU) and a total of 56 RUs were investigated.

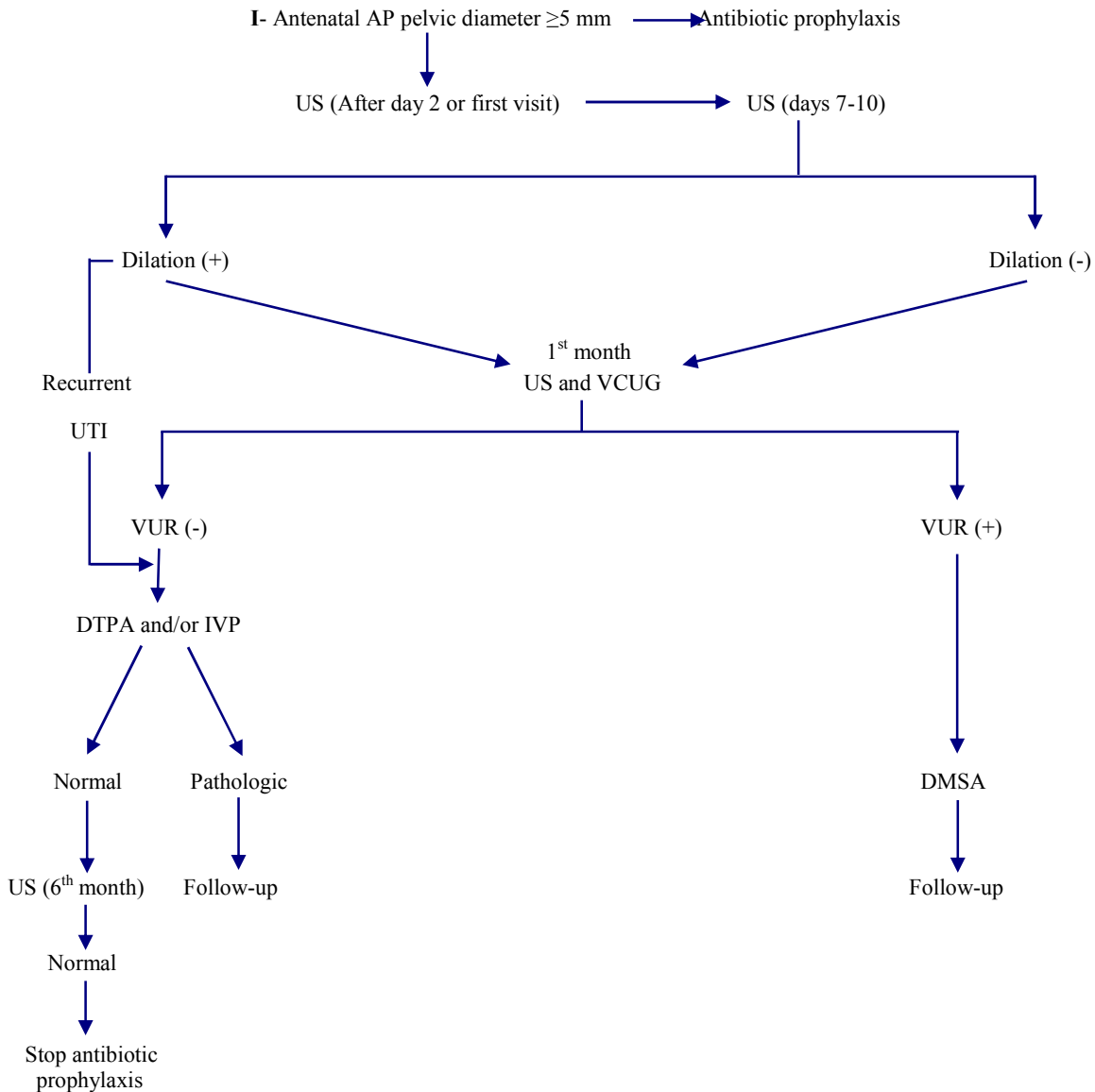
Patients included in the study were evaluated according to our previously proposed protocol^[5]. Fig. 1 shows the simplified algorithm for postnatal evaluation of infants with prenatally detected AH. Hydronephrosis was defined as the dilation of the anteroposterior pelvic diameter (APPD) of the fetal renal pelvis ≥ 5 mm after 20

weeks of gestation. Regardless of the gestational phase, infants diagnosed as having AH were followed up. Postnatal US (Toshiba SSA-270A color Doppler) examination was performed on the third day of life or when first seen. Initial urine samples were taken from each patient for culture before prophylactic antibiotic treatment was started with 10 mg/kg/night dosage of amoxicillin. We were not able to convince the families for urine sampling with urinary catheter or suprapubic aspiration, therefore, the urine was sampled by applying a urine bag in girls, from front to back at vulva and perineum, and in boys, after pulling the prepuce back and wiping with antiseptic solution. The urine bags were changed in half an hour's period if the infant had not urinated. Urine cultures were repeated monthly to enable early detection and treatment of infections. In the presence of bacteriuria with clinical findings, antibiotic treatment was started. Urine culture was repeated 3 days after completion of the treatment^[6].

Regardless of the initial US result, a second US examination was performed on day 10. A third US was performed in the first month of life. In all patients, micturating cystourethrography (MCUG) (Siemens model 1801091x1060) was performed at the end of the first month. Briefly, the area was cleaned and a catheter was placed into child's bladder. The catheter was connected to a bottle of iodinated contrast material that was visualized on the x-ray screen. After the bladder was filled up with contrast material through urinary catheter, images were obtained.

Reflux grading was performed according to international VUR classification system. Grades I, II and III were considered low grade and Grades IV and V high grade reflux. Patients with posterior urethral valve and neurogenic bladder were excluded from the study. A DMSA (Millenium manufactured MPR) scan was performed to assess the renal damage. Renal scarring score was graded according to the following classification system^[7]:

- Type 1: renal lesion with two or less scars
- Type 2: renal lesion with more than two scars
- Type 3: generalized renal damage, total uptake $>10\%$
- Type 4: end stage, atrophic kidney, total uptake $<10\%$



II- On admission: routine urinalysis, urine culture, serum urea, serum creatinine and monthly urine culture

III- Follow-up: surgery decision, medical treatment

Fig. 1: Simplified algorithm for postnatal evaluation of infants with prenatally detected hydronephrosis (US: Ultrasonography, VCUG: Voiding cystourethrogram, VUR: Vesicoureteral reflux, DMSA: ^{99m}Technetium-dimercaptosuccinic acid scan, DTPA: ^{99m}Technetium-diethylene triamine penta-acetic scan, IVP: Intravenous urogram, UTI: Urinary tract infection)

Indications for surgery were the presence of multiple scars and/or development of new scars or frequently recurrent UTI or persistent UTI in patients with high-grade VUR.

Height and weight standard deviation scores (HSDS and WSDS) were calculated to assess growth and development; weight-for-height (relative weight) was calculated to assess nutritional status of the infants. These parameters were calculated every three months

for the first 18-month-period and every six months for the rest of the follow-up period^[7].

Statistical analyses were performed using t-test and Chi-squared tests. $P < 0.05$ was accepted as significant.

This study was approved by our Institutional Review Board. Parents were informed by explaining the clinical significance of urinary tract abnormalities as well as the rationale of postnatal follow-up.

Findings

Of 277 patients (340 RUs) with hydronephrosis diagnosed by prenatal US, 36 (13%) (56 = 16.5% RUs) were detected to have VUR.

Twenty-five (69.4%) of these patients were males, 11 (30.6%) females, and the male-female ratio was 2.5. Average follow-up duration was 37.8±24.5 months (min 12 months, max 72 months). Mean gestational age at intrauterine (IU) diagnosis was 31.5±6.8 weeks (min 16 weeks, max 39 weeks). Mean IU renal pelvic anteroposterior diameter was 11.4±5.16 mm.

Mean pelvic anteroposterior diameter was measured as 5-9 mm in 25 (44.7%), 10-15 mm in 22 (39.3%), and >15 mm in 9 (16%) affected RUs. Table 1 presents the demographic features of these patients.

The distribution of RUs and grades of postnatally detected VUR in relation to renal pelvic anteroposterior diameters are given in Table 2. There was no significant correlation between renal pelvic anteroposterior diameter measured by antenatal US and VUR grade detected in the postnatal period ($P>0.05$).

Furthermore, although 5 (13.8%) out of 36 cases with postnatally detected VUR had normal US results in weeks 1 and 4, one patient had grade II, 3 had grade III, and 1 had grade IV VUR.

Of 17 patients who had intrauterine fetal renal pelvic diameter between 5-9 mm, 4 (23.5%)

patients were admitted to surgery, 3 cases (17.7%) are still under medical observation and 10 (58.8%) cases showed recovery by medical treatment. Among patients with fetal renal pelvic anteroposterior diameter between 10-15 mm ($n=14$ patients), 6 (42.8%) required surgery, while 7 (50%) recovered by medical therapy and 1 case (7.2%) is still under medical observation.

All patients who had a fetal renal pelvic anteroposterior diameter more than 15 mm ($n=5$ patients), underwent surgical treatment ($P<0.05$)(Table 3).

A comparison between patients treated medically and requiring surgery in the postnatal period is given in Table 4. The mean IU renal pelvic diameter was significantly higher in infants admitted to surgery in the postnatal period (14.71±7.16) than in infants who showed recovery by medical treatment (8.0±2.1) and in those who are still on medical follow-up (10.06 3.21)($P<0.05$). The mean age of patients at the time of surgery was 18.5±15.9 months and the mean postoperative follow-up duration was 19.3±8.5 months. Although statistically insignificant, the frequency of UTIs was higher in the medically treated group than in the surgery group (1.42±1.27 and 0.9±0.69 episode/year, respectively)($P>0.05$). Both initial and final DMSA scans showed significantly more damage in patients admitted to surgery than in medically treated cases ($P<0.05$). Although infants who

Table 1: Demographic features of the patients

Parameter	Number	%
Number of cases/renal units	36 / 56	
Female	11 / 16	30.5 / 28.5
Male	25 / 40	69.4 / 71.4
Male/Female	2.5	
Mean duration of postnatal follow-up period (months)	37.8±24.5	
Minimum	12	
Maximum	72	
Mean gestational age at AH diagnosis (weeks)	31.5±6.8	
<30	11	30.5
30-35	5	13.8
>35	20	55.7
Mean IU pelvic diameter (mm)	11.4±5.16	
5-9	25	44.7
10-15	22	39.3
>15	9	16
Median time of postnatal admission (days)	5.5	
Frequency of UTIs (episode/year)	1.25±0.83	

IU: intrauterine/ AH: antenatal hydronephrosis/ UTI: urinary tract infection

Table 2: Comparison between intrauterine renal pelvic anteroposterior diameter and vesicoureteral reflux grades in renal units ($P>0.05$)

Intrauterine renal pelvic anteroposterior diameter	Grade II VUR n (%)	Grade III VUR n (%)	Grade IV VUR n (%)	Grade V VUR n (%)
5-9 mm (25 RUs)	1 (1.7)	18 (32.2)	3 (5.3)	3 (5.3)
10-15 mm (22 RUs)	5 (8.9)	0	3 (5.3)	14 (25)
>15 mm (9 RUs)	2 (3.7)	0	5 (8.9)	2 (3.7)
Total (56 RUs)	8 (14.3)	18 (32.2)	11 (19.5)	19 (34)

VUR: vesicoureteral reflux; RUs: renal units

required surgery in the postnatal period showed poorer initial growth and development scores (HSDS: -0.17 ± 0.86 and WSDS: 0.00 ± 0.14) as well as nutritional status (RW: 93.63 ± 11.34) than medically treated patients (HSDS: 0.28 ± 0.34 , WSDS: 0.12 ± 0.23 and RW: 98.19 ± 8.81), the differences were not statistically significant ($P>0.05$). Although insignificant, in patients who underwent surgery, these parameters improved gradually at the final evaluation ($P>0.05$).

Discussion

Postnatal management and follow-up of infants with antenatally detected hydronephrosis requires time, effort, family support and adequate finances. Furthermore, because most of the methods are interventional and entail exposure to low dosage radiation, there are ongoing ethical debates about how to proceed^[5]. Numerous studies have examined the short- and intermediate-term outcomes of children diagnosed with AH, and VUR has been reported in approximately 10–20%^[8-11]. A total of 277 patients that had a renal pelvic anteroposterior diameter of 5 mm or greater at any gestational phase were included in our study. MCUG was

performed in every patient, even when the week 1 and week 4 US results were normal^[5]. VUR was detected in 36 (13%) patients.

Measurement of the renal pelvic anteroposterior diameter is the simplest and most sensitive technique for prenatal diagnosis of congenital hydronephrosis^[12]. Although pelvic diameter detected antenatally is associated with pathology in the postnatal phase, it does not provide preliminary information regarding pathology to be detected^[5,13]. Although the likelihood of pathology increases with increasing APPD, to date there is no consensus on the optimal APPD threshold for determining the need for postnatal follow-up^[14]. Indeed, in our prior study^[5], we studied 156 infants (193 kidney units) whose scan showed that one or both APPDs were 5 mm or greater at >20 weeks. In 84 of 193 kidney units, intrauterine pelvic dilation was 5–9 mm. Among these, 27 (32%) kidney units were normal and 57 (68%) pathological. Of the 57 kidney units with urinary tract abnormality, 12 (15%) were treated surgically.

Of these 12 kidney units, 9 (75%) were detected to have VUR. Therefore, we suggested that all babies whose routine antenatal scan showed that one or both APPDs were 5 mm or more should continue to be observed. This study supported the findings of other studies that

Table 3: Current state of the patients and their intrauterine renal pelvic anteroposterior diameters (n=36 patients)

Final assessment	5-9 mm n (%)	10-15 mm n (%)	>15mm * n (%)
Normal after surgery	4 (23.5)	6 (42.8)	5 (100)
Still on medical follow-up	3 (17.7)	1 (7.2)	-
Normal after medical treatment	10 (58.8)	7 (50.0)	-
Total number of patients	17 (100)	14 (100)	5 (100)

* Significantly more patients with IU renal pelvic anteroposterior diameter >15 mm required surgery ($P<0.05$)

Table 4: Comparison between cases that required surgery and cases who received medical treatment

	Required surgery	Received medical treatment	P. value
Number of cases (%)	15 (41.7)	21 (58.3)	
Number of renal units (%)	23 (41)	33 (59)	
Postnatal follow-up period (months) (mean±SD)	48.5±22.3	33±26.9	0.10
Male /Female	11/4	14/7	0.83
Mean IU renal pelvic diameter (mm)	14.71±7.16	10.06±3.21	0.02
Frequency of UTIs (episode/year)	0.9±0.69	1.42±1.27	0.65
No. of units affected at initial DMSA, (%)	10 (43.4)	6 (18.1)	0.02
No. of scarred units at final DMSA (%)	8 (34.7)	4 (12.1)	0.03
VUR recovery period (months) (mean±SD)	17.2±8.5	11.25±4.9	0.54
Height SDS - initial evaluation (mean±SD)	-0.17±0.86	0.28±0.34	0.21
Height SDS - final evaluation (mean±SD)	0.13±0.57	0.54±1.13	0.47
Weight SDS - initial evaluation (mean±SD)	0.00±0.14	0.12±0.23	0.65
Weight SDS - final evaluation (mean±SD)	0.54±1.13	0.45±0.84	0.19
RW - initial evaluation (mean±SD)	93.63±11.34	98.19±8.81	0.34
RW - final evaluation (mean±SD)	98.37±12.21	101.97±14.85	0.42

IU: intrauterine/ UTI: urinary tract infection/ DMSA: ^{99m}Tc-Technetium-dimercaptosuccinic acid scan/
SDS: standard deviation score/ RW: relative weight

showed a correlation between urinary tract abnormality and APPD measurement as low as 5 mm and suggested that it is not possible to determine a normal upper limit for the antenatal renal pelvis^[12,13].

While an increase in intrauterine renal pelvic anteroposterior diameter suggests that there may be a severe obstructive uropathy, this finding is inadequate for predicting VUR occurrence and its severity^[5]. Although some authors have suggested that MCUG is not ethical to perform as being too invasive for mild hydronephrosis, others have thought that a normal postnatal US could not preclude the presence of urinary tract abnormality. This argument continues today due to ethical debates.

Marra et al^[15] suggest a MCUG for patients with a renal pelvic anteroposterior diameter of 5 mm or greater. However, other authors suggest that MCUG should be performed when a greater renal pelvic dilatation is detected^[16].

Another study^[17] states that a MCUG is not needed for patients with two subsequent normal US results. Nevertheless, Tiballs et al^[18] and Mohammadjafari et al^[19] argue that the assessment of VUR should be performed for all cases with antenatal hydronephrosis. We also believe that postnatally all antenatal hydronephrosis infants should be evaluated by MCUG. This policy, to our opinion, will help to identify VUR cases before occurrence of UTI and

reduce the risk of further renal injury. In fact, among 36 patients that were detected to have VUR in this study, 5 (13.8%) had normal postnatal US results in the first week and first month. However, 4 of these cases had low grade VUR, and 1 had high grade VUR. This finding, therefore, suggests that normal postnatal US results do not exclude VUR and all patients with antenatal hydronephrosis should be subjected to MCUG. Also, a relationship between IU renal APPD and VUR grade was not found in our study.

Patients with no antenatal history and diagnosed postnatally by VUR due to recurrent UTIs, predominantly in girls, usually show moderate disease^[20]. On the other hand, most of the patients with antenatal hydronephrosis who were detected to have VUR in the postnatal phase are mainly boys. As in our series, many other studies suggest that male sex is a risk factor for VUR^[5,21,22,23].

As the child grows, reflux may spontaneously recover. Although the spontaneous resolution rate decreases with increasing severity of reflux, resolution can be seen even in cases of high grade VUR^[24].

Spontaneous VUR resolution has been detected in 56% of patients with antenatal hydronephrosis that were diagnosed with VUR in the postnatal period. Specifically, spontaneous VUR recovery was found to occur in 72% of low grade cases and 9% of high grade cases^[22].

Meanwhile, Yeung et al^[20] reported a resolution rate in 70% of low grade and 43% of high grade VUR cases. In our study, we observed a 47.2% recovery rate for VUR patients who were on medical treatment.

In the postnatal period, infants with reflux previously detected to have a prenatal pelvic dilatation usually show renal damage, possibly congenital, at the time of diagnosis. However, renal damage is claimed to progress after UTIs^[23,24]. Recurrent UTIs, pressure caused by reflux of sterile urine and intrarenal reflux are recognized as causes of renal parenchymal defects in infants with VUR^[25,26]. In our study, initial DMSA scans showed hypoactive lesions in 16 (28.5%) of 56 RUs and the figure decreased to 21.4% (12 RUs) at the final DMSA. No damage appeared later during the follow-up period in any of the patients. This recovery in the DMSA underscores the importance of early diagnosis of VUR and close follow-up with a multidisciplinary approach.

The literature on postnatal follow-up of cases with prenatal hydronephrosis mostly focuses on diagnosis of the disease and treatment options; therefore, there is limited information on growth, development and nutritional parameters of these patients. Main reasons of growth retardation in these infants are increased catabolism and lack of appetite caused by frequent UTIs and tubulointerstitial dysfunctions associated with intrauterine hydronephrosis. It has been reported that growth and development of infants with antenatal hydronephrosis are not negatively affected by close postnatal follow-up and by appropriate medical or surgical treatment and even in growth retarded infants catch-up growth is observed^[27]. There is a consensus that timely diagnosis of UTIs by close follow-up, decrease in number of UTIs by antibiotic prophylaxis, if necessary, preventing delay of surgical treatment avoid increased catabolism and lack of appetite, enabling normal growth and development^[4,27,28]. In our study, all patients with prenatal hydronephrosis were treated with antibiotic prophylaxis and closely followed-up. Both weight and height SDS parameters of all cases remained within normal range during the follow-up period. At the final evaluation, height and weight SDS and average

RW scores were observed to have increased compared to initial evaluation; however, the difference was not significant ($P>0.05$).

In recent years, due to diagnostic and therapeutic interventions as well as by close follow-up starting from newborn stage extending to early infancy, there has been a decrease in number of cases of ESRF resulting from UTIs, especially in cases with urinary system malformation, in many developed countries. In Turkey, recurrent UTIs, especially in conjunction with urinary malformations are still the main reasons of ESRF due to a lack of follow-up protocols for prenatal, newborn and early infancy stages^[29].

There are some limitations in our study. First, we did not perform prenatal grading. Also, the timing of AH diagnosis is not universal. We defined hydronephrosis as the dilation of the APPD of the fetal renal pelvis ≥ 5 mm after 20 weeks of gestation. Second, although a lack of consensus exists concerning the need for a postnatal MCUG in all AH cases regardless of the US findings, we routinely performed a MCUG in all infants with AH.

Conclusion

The performance of MCUG at the first month of life in infants with antenatally detected hydronephrosis enables earlier diagnosis of VUR. By detection of these VUR cases and close postnatal follow-up, frequent UTIs and associated problems can be prevented and therefore, normal growth and development can be achieved. Moreover, medical or surgical, if necessary, treatment may prevent renal parenchymal scarring, precluding chronic renal failure. However, further large-number, multicenter and prospective studies are needed to clarify this issue.

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Conflict of Interest: None

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