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CLINICAL RESEARCH



ificity was 73.8%. **Conclusions:** Patients with SFU grade 2 hydronephrosis require long-term follow-up. Surgery and close postsurgical observation may be necessary for patients with SFU grade 3 and 4 hydronephrosis. An initial B-mode ultrasound screening at 7-10 days after birth may help make an optimal diagnosis and treatment selection.

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Background

Hydronephrosis is a common congenital condition that can be detected by prenatal ultrasound [1,2]. The frequency of prenatal hydronephrosis diagnosed by ultrasound has been reported to be 0.6–5.4% of newborns [3–9]. Among infants with hydronephrosis, both kidneys are affected in 17–54% of the cases [10–12]. Hydronephrosis has been reported to be transient or physiological in nature (41–88%) or secondary to pelviureteric junction obstruction (10–30%), vesicoureteric reflux (10–20%), vesicoureteric junction obstruction (5–10%), multicystic dysplastic kidney (4–6%), duplex kidney with or without ureterocele (2–7%), and posterior urethral valves (1–2%) [13].

Nevertheless, the detection of fetal hydronephrosis by ultrasound presents a dilemma in terms of diagnosis and treatment, and there is considerable debate and controversy regarding the optimal management of children with prenatally-diagnosed hydronephrosis [3,14,15]. A recent report highlighted the substantial variations in the use of grading criteria for the diagnosis of fetal hydronephrosis and in the management of mild prenatal hydronephrosis [16]. Hence, antenatal hydronephrosis does not necessarily indicate the presence of an obstruction or poor renal function. Indeed, most of the cases of antenatal hydronephrosis resolve spontaneously by the time of birth or during infancy period [10,12,17,18]. The pediatric surgeon thus faces the challenge of distinguishing the affected infants who require long-term observation or surgical intervention from those who do not require observation or intervention. Postnatal ultrasound is considered a critical investigation tool used to follow affected infants to monitor the progression of the disease, and can be complemented by other investigations such as micturating cystourethrography (MCU) and diuretic renography.

Therefore, in order to shed some light on the diagnosis and management of antenatal hydronephrosis, the present study aimed to examine the postnatal follow-up and treatment for hydronephrosis diagnosed prenatally in a pediatric hospital in China.

Material and Methods

Study design

This was a retrospective study of infants prenatally diagnosed with hydronephrosis and treated at the Department of Pediatric Surgery of Qilu Hospital, Shandong University (China) between January 2005 and December 2013. The study was approved by the Ethics Committee of Qilu Hospital. The need for individual consent was waived by because of the retrospective nature of the study.

Patients

Patients were diagnosed with antenatal hydronephrosis without dilatation of the ureter. Exclusion criteria were: (1) patients with SFU grade 4; (2) ipsilateral or contralateral reflux; (3) solitary kidney; (4) pelvic stones; (5) ureteral dilatation; 6) anatomical or neurogenic abnormality of the lower urinary tract; or (7) abnormality other than ureteropelvic junction obstruction of the contralateral normal kidney

Imaging

All patients underwent initial assessment of hydronephrosis by ultrasound one week after birth and underwent standardized DTPA renography one month after birth. The maximum anteroposterior diameter (APD) of the renal pelvis was measured on a transverse renal image. Parenchymal thickness was measured at upper, middle, and lower poles, and the maximum parenchymal thickness was used as a variable. The Society for Fetal Urology (SFU) grading system was used for hydronephrosis4[19-21] as well as the method designed by Grignon et al. [22] (Table 1). Infants who had an ultrasound within 72 hours of birth because of an emergency clinical status were re-evaluated at one week of age. For diuretic renogram, oral hydration was started two hours before the scan; intravenous DN/2 was started at 15 mL/kg over 30 minutes, beginning 15 minutes before injection of the radiotracer, and then at 4 mL/kg/hour for the remaining of the study. The study was performed in the supine position with a bladder catheter. Furosemide 1 mg/kg was injected at the start of the study and renal function was measured, along with assessment of isotope washout after diuresis. During the diuresis phase, the patient was shifted to the prone position. Some patients were additionally investigated using emission computed tomography (ECT) and magnetic resonance urography (MRU).

Biochemistry

Urinary and blood urea nitrogen (UUN, BUN) and urinary and serum creatinine (Cr) were measured routinely.

Treatments and follow-up

Patients with SFU grade 1 hydronephrosis (equivalent to pyelectasis \leq 1.5 cm in Grignon's approach; Table 1) had followup with B-mode ultrasound. A regular follow-up examination to clarify the pathological obstruction was deemed necessary in patients with SFU grade 2 hydronephrosis (expanded renal pelvis of >1.5 cm). Patients diagnosed with SFU grade 3 hydronephrosis were closely followed due to the possibility of obstructive pathological factors and permanent renal damage. The ECT and MRU investigations were carried out at one month of age, and ultrasound examinations were undertaken

	SFU method	Grignon's method				
Grade	Characteristics	Grade	Characteristics			
0	The central renal echo complex is closely apposed	1	Pyelectasis <1 cm			
1	There is slight separation of the central renal echo complex	2	Pyelectasis ≥1 cm and ≤1.5 cm			
2	The renal pelvis is further dilated and a single or a few calices may be visualized	3	Pyelectasis >1.5 cm; slight dilatation of the rena calices.			
3	The renal pelvis is dilated and there are fluid- filled calices throughout the kidney. The renal parenchyma is of normal thickness	4	Pyelectasis >1.5 cm; moderate dilatation of the renal calices.			
4	As Grade 3, but the renal parenchyma over the calices is thinned	5	Pyelectasis >1.5 cm; severe dilatation of the renal calices; the renal parenchyma over the calices is thinned			

Table 1. Grading of fetal hydronephrosis using the Society of Fetal Urology (SFU) guidelines and Grignon's method.

Table 2. Characteristics of the patients.

		N	%
Sex	Male	119	56.7
JEX	Female	91	43.3
	Left	140	66.7
Affected side	Right	60	28.6
	Bilateral	5	2.4
Age at surgery (month)	24 (2–36)		
	Grade 1	125	59.5
SFU grade 1 week after birth	Grade 2	74	35.2
	Grade 3	11	5.2
APD 1 week after birth	0.8 (0.1–3.1)		
Parenchymal thickness 1 week after birth (mm)	6 (2.7–7)		
	Grade 1	104	49.5
CELL grade at last fellow up	Grade 2	77	36.7
SFU grade at last follow-up	Grade 3	10	4.8
	Grade 4	19	9.1

APD – maximum anteroposterior diameter.

every two to four weeks. Surgery was performed at the time of presentation if the initial differential renal function (DRF)was <35%, with an obstructed curve on renogram and/or parenchymal thickness below 3.5 mm. Post-surgery, the patients were closely monitored by ultrasound and followed at one, three, six, and 12 months. Antibiotics were not used during follow-up. Renogram and MCU were not performed after surgery. The other patients were followed using a standard protocol, with ultrasound and radionuclide studies being performed every three months during the first two years. If renal function and

SFU grade remained stable, the patients were followed by ultrasound every six months for another two years. All patients were followed for at least two years after birth.

Statistical analysis

Normally distributed continuous variables are presented as mean \pm standard deviation (SD) and were analyzed using the Student's t test or ANOVA with the Tukey's post hoc test, as appropriate. Non-normally distributed continuous variables

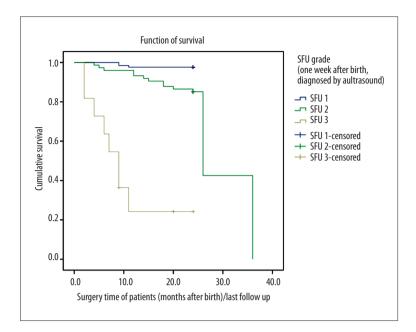


Figure 1. Kaplan-Meier curves of the occurrence of surgery according to the SFU grade determined by ultrasound one week after birth.

Table 3. Univariate analyses for the occurrence of surgery in patients with hydronephrosis.

	No surgery (n=183)		Surgery (n=27)		Р
Gender					
Male	104	(56.8)	15	(55.6)	0.601
Female	79	(43.2)	12	(44.4)	
SFU grade 1 week after birth					<0.001
Grade 1	122	(66.7)	3	(11.1)	
Grade 2	60	(32.8)6	14	(51.9)	
Grade 3	1	(0.6)	10	(37.0)	
APD (cm) 1 week after birth	0.7	(0.1–2)	1.7	(0.35–3.10)	<0.001
Parenchymal thickness (mm) 1 week after birth	6	(5–7)	5	(2.7–7)	<0.001
Last SFU grade					0.987
Grade 1	104	(56.8)	0		
Grade 2	77	(42.1)	0		
Grade 3	2	(1.1)	8	(29.6)	
Grade 4	0		19	(70.4)	

APD – maximum anteroposterior diameter.

are presented as median (range) and were analyzed using the Mann-Whitney test. Categorical variables are presented as frequencies and were analyzed using the Fisher exact test. The occurrence of surgery during follow-up was analyzed using Kaplan-Meier curves, which were analyzed by the log-rank test. A multivariate analysis using Cox regression analysis was performed to identify the independent factors involved in the occurrence of surgery. The receiver operating characteristic (ROC) curve approach was used to determine the accuracy of factors associated with the occurrence of surgery. SPSS 16.0 (IBM, Armonk, NY, USA) was used for analysis. Two-sided p-values <0.05 were considered statistically significant.

Table 4. Multivariate analysis for the occurrence of surgery in patients with hydronephrosis.

	HR	95	%СІ	Р
SFU grade of one week after birth				0.066
SFU grade 2 of one week after birth	3.237	0.837	12.521	0.089
SFU grade 3 of one week after birth	9.230	1.426	59.744	0.020
APD of one week after birth	2.806	1.110	7.095	0.029
CT (mm) of one week after birth	0.416	0.243	0.712	0.001

APD – maximum anteroposterior diameter.

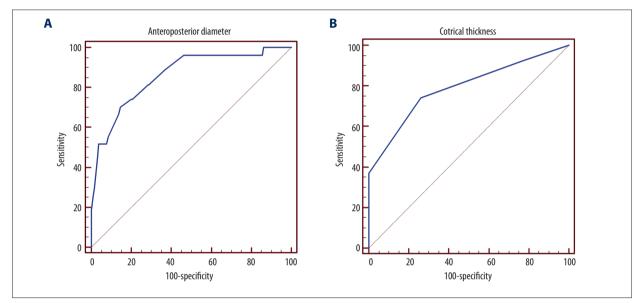


Figure 2. ROC curve for anteroposterior diameter (A) and parenchymal thickness (B).

Results

Characteristics of the patients

Between January 2005 and December 2013, 210 patients were treated for neonatal hydronephrosis. Table 2 presents the characteristics of the patients. Most patients (59.5%) were SFU grade 1. At the last follow-up, some patients had progressed. Twenty-seven patients underwent surgery.

Surgery

Figure 1 presents the Kaplan-Meier curves of the occurrence of surgery according to the SFU grade determined one week after birth by ultrasound. Only a small proportion of patients who were originally grade 1 underwent surgery (n=3), while most grade 2–3 patients underwent surgery.

Univariate analyses

Table 3 presents the characteristics of the patients according to the occurrence of surgery. Patients who underwent surgery were more often SFU grade 2 or 3 (p<0.001), had a larger APD (p<0.001), and had a smaller parenchymal thickness (p<0.001).

Multivariate analysis

The variables that were significant in univariate analyses were included in a multivariate model (Table 4). Results showed that SFU grade 3 (HR=9.23, 95% CI: 1.43-59.74, p=0.02), APD (HR=2.81, 95% CI: 1.11–7.10, p=0.03), and parenchymal thickness (HR=0.42, 95% CI: 0.24–0.71, p=0.001) were independently associated with the occurrence of surgery.

ROC analysis

Figure 2 presents the ROC curve analysis for the accuracy of APD and parenchymal thickness for predicting the occurrence

of surgery. For APD, using a cut-off point of 1.1, the area under the curve (AUC) was 0.86, Youden index was 0.556, sensitivity was 70.4%, and specificity was 85.3%. For parenchymal thickness, using a cut-off point of 5, AUC was 0.79, Youden index was 0.478, sensitivity was 74.1%, and specificity was 73.8%.

Discussion

Hydronephrosis is a common congenital condition that can be detected by prenatal ultrasound [1,2], but there is considerable debate and controversy regarding the optimal management of children with prenatally-diagnosed hydronephrosis [3,14,15]. Therefore, this study aimed to examine postnatal follow-up and treatment for hydronephrosis diagnosed prenatally, as well as the characteristics associated with the occurrence of surgery. Results showed that 2.4%, 18.9%, and 90.9% of patients with SFU grade 1, 2, and 3 hydronephrosis, respectively, underwent surgery. SFU grade 3, APD, and parenchymal thickness were independently associated with the occurrence of surgery. For anterioposterior diameter, using a cut-off point of 1.1, sensitivity was 70.4%, and specificity was 85.3%. For parenchymal thickness, using a cut-off point of 5, sensitivity was 74.1%, and specificity was 73.8%.

Before the recent advances in prenatal ultrasound, the diagnosis of hydronephrosis was often incidental. However, the recent developments in ultrasound and prenatal medical technologies have allowed for the diagnosis of hydronephrosis during the fetal period, and its monitoring after birth. Studies [1,2] are now available concerning the management of hydronephrosis in children, and guide clinicians to make better decisions regarding the selection of suitable follow-up strategies and surgical interventions.

The etiology of fetal hydronephrosis may be either physiological or pathological. Physiological hydronephrosis often spontaneously regresses by itself. Indeed, compared with a newborn, a fetus has a relatively low renal vascular resistance and a relatively high renal blood flow, and the combination of a higher glomerular filtration rate and a lower renal concentrating capacity may thus lead to a relatively high urine volume. In addition, as the compliance of the ureter increases, it becomes easier to expand. Since the fetal and neonatal kidneys are not fully developed, the renal medullary cone may be transparent under ultrasound examination, which leads to a wrong diagnosis of hydronephrosis. In contrast, pathological hydronephrosis is due to renal obstruction, resulting in the separation of the collection system. Since the fetal and neonatal renal tubules are relatively short and straight, the consequences of obstruction are more serious than in the adult. Hence, it is very important to distinguish between physiological and pathological hydronephrosis, since their management is different.

Ultrasound investigations that ate carried out during prenatal screening and subsequent follow-up after birth, are the primary and preferred means of monitoring patients diagnosed with hydronephrosis. Although ultrasound has a limited role in predicting the degree of renal impairment and identifying the cause of the restriction/obstruction, it is highly useful for the diagnosis of hydronephrosis and evaluation of disease progression. Early studies [23,24] have shown that the patients with renal parenchyma thickness >4 mm had normal glomerular, tubular, and cell structure; at 3 mm thickness of renal parenchyma, some surviving glomeruli and tubules were evident but there was cell deformation with the presence of abnormal nuclei, and removal of the obstruction resulted in partial restoration of the cell morphology; at 2 mm, glomerular and tubular structures were not apparent, and the normal cell structure was not evident through electron microscopy. After a gestational age of 24 weeks, ultrasound is able to demonstrate clearly the structure of the fetal kidney, enabling direct measurement of the collection system, the expansion of the renal pelvis, and the thickness of the renal cortex. Since it is a non-invasive and straightforward technique, it has an advantage over other methods such as ECT, MRU, and intravenous pyelography, particularly in young children.

An APD of 4 mm or greater at 20 weeks of gestation or larger threshold of 7 mm in the third trimester has been used as an indicator for the diagnosis of prenatal hydronephrosis [14]. In addition to diagnosis of the condition, antenatal ultrasound has also been reported to have some prognostic value. Interestingly, the second and third trimester APD cut-offs of 5 mm and 8 mm to10 mm, respectively, have been reported to have 100% sensitivity for predicting the requirement for postnatal surgery [25]. Similarly, in another study, APD thresholds of 10 mm at 20 weeks and 12 mm at 30 weeks of gestation were found to have 100% sensitivity, and 86% and 67% specificity (respectively) for the diagnosis of hydronephrosis postnatally [26]. The risk of postnatal pathology increases with the severity of prenatal hydronephrosis [10], while antenatal APD of <12 mm is associated with stabilization or resolution in 98% of the infant population with hydronephrosis [27]. In this study, using an APD cut-off of 1.1 had 70.4% sensitivity and 85.3% specificity for the occurrence of surgery. Using parenchymal thickness of 5 mm had 74.1% sensitivity and 73.8% specificity.

The SFU guidelines recommend that all children with a prenatal diagnosis of hydronephrosis should be investigated with an ultrasound within one week of birth, and the results should be compared with the last prenatal ultrasound, in order to determine the classification of the hydronephrosis. Docimo et al. [28] have reported that ultrasound examination 48 hours after birth showed either no hydronephrosis or a mild hydronephrosis with no obvious significant obstructive renal injury at one year. However, Wiener et al. [29] have reported that the grading of hydronephrosis using an ultrasound examination two days after birth may differ from the ultrasound examination 7–10 days after birth, possibly due to the presence of oliguria in the first few days. Hence, the premature use of an ultrasound investigation may underestimate the hydronephrosis grade. Urinary tract abnormalities have been found more specifically six weeks after birth. The present study suggests that an initial B-mode screening 7–10 days after birth with a second investigation 42 days after birth could be a good approach, but severe cases may be investigated earlier. The hydronephrosis may then be graded based on these investigations, and an appropriate management approach can be selected.

There is still some controversy regarding the treatment of young infants with hydronephrosis. Some authors believe that the majority of young infants with mild-to-moderate hydronephrosis may be managed by observation rather than surgery. A previous study showed that there was a recovery rate of 98% in infants with SFU grade 1 or 2 hydronephrosis or APD <12 mm, compared with 51% recovery with grade 3 or 4 hydronephrosis or APD >12 mm [25]. In addition, the SFU reported that surgery was eventually needed in 25% of children aged <6 months with grade 3-4 hydronephrosis and a relative renal function >40% [30]. Furthermore, surgery was found to reduce the degree of hydronephrosis and improve the renal pelvis evacuation, and was superior to the conservative approach of close observation. Maizels et al. [31] reported that almost all children with grade 3-4 hydronephrosis required surgery: in a review of 464 medical records, the vast majority of patients receiving surgery had grade 3 or 4 hydronephrosis with an evidence of obstruction (renography), whereas those managed by observation tended to have grade 2 or 1 disease without obstruction. Consistent with these data, a recent retrospective review of 629 infants found that the proportion of patients requiring

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surgery for grade 1, 2, 3, and 4 hydronephrosis was 0,% 13%, 70%, and 100%, respectively [32]. In clinical practice, the decision to go ahead with surgical intervention, and its timing, are based on the following main considerations: (1) SFU grade 3–4; (2) continued expansion of the renal pelvis collection system; (3) a renal cortex <5 mm; and (4) a single-kidney decrease in GFR, as reflected by ECT and MRU examinations.

Our study is not without limitations. The sample size was limited and from a single center. The retrospective design prevented us fron examining factors that were not routinely collected. Multicenter studies should be performed to improve our understanding of fetal hydronephrosis. Future research should be directed at improving the understanding of areas where knowledge remains limited such as the renal processes underlying physiological and pathological hydronephrosis and their progression or resolution, and the optimization of the point at which surgical intervention is deemed necessary.

Conclusions

It is important to standardize the guidelines based on up-todate research, to help clinicians to make better decisions regarding the management of infants with a prenatal diagnosis of hydronephrosis. In conclusion, patients with SFU grade 2 hydronephrosis require long-term follow-up. Surgery and close postsurgical observation may be necessary for patients with SFU grade 3 and 4 hydronephrosis. An initial B-mode ultrasound screening at 7–10 days after birth may help making an optimal diagnosis and treatment selection.

Conflict of interest

The authors declare that they have no conflict of interest.

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