REVIEW ARTICLE

Management of Infants Diagnosed with Antenatal Hydronephrosis and Determining the Need for Surgical Intervention

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ABSTRACT

Antenatal hydronephrosis (ANH) is the most common pathology in the fetal period. The cause of ANH ranges from intrauterine transient hydronephrosis to clinically severe congenital anomalies of the kidney and urinary tract. Coexistence with oligohydramnios, ectopic kidney, and extrarenal anomalies in the prenatal period supports the existence of important pathology. Ultrasonography should be performed on all babies with ANH in the postnatal period, and the follow-up of the patients should be done according to the anteroposterior renal pelvic diameter and the grading recommended by the Society for Fetal Urology. Surgical intervention is vital according to some criteria in patients with progressive hydronephrosis and vesicoureteral reflux.

Key words: Antenatal hydronephrosis, surgical intervention, vesicoureteral reflux

DEFINITION

Hydronephrosis is swelling of one or both kidneys. Hydronephrosis occurs as a result of enlargement of the renal pelvis and/or calyces. In infants diagnosed with hydronephrosis before birth, this condition is defined as antenatal hydronephrosis (AHN).[1]

ETIOLOGY

Many pathological conditions can cause AHN. AHN can occur due to or without a urinary tract anomaly. AHN without urinary tract anomaly has been termed isolated ANH (IAHN). IAHN is the etiology in the majority of infants with hydronephrosis. IAHN is believed to result from a physiological expansion of the developing ureter. The etiology of IAHN has not been fully elucidated, and additional studies are needed for this.[2]

Approximately 60% of AHNs are temporary and physiological hydronephrosis. Although ureteropelvic junction obstruction and vesicoureteral reflux (VUR) the most common urinary tract anomalies, the pathologies shown in Table 1 can be observed.[3]

EPIDEMIOLOGY

Hydronephrosis is the most common pathological finding in the urinary tract in antenatal screening performed by fetal ultrasonography (US) and constitutes 50% of all congenital anomalies. In studies conducted, it was found that 0.6–1.4% of fetuses had AHN. The incidence of a significant uropathy in association with hydronephrosis is 0.2%. Male/female ratio is 2/1 and 20–40% of the cases are bilateral. There is a positive family history of up to 8% (renal agenesis, multicystic kidney, polycystic kidney, and reflux nephropathy) in affected fetuses. It is stated that the rate of urological diseases requiring surgical intervention is between 4.1 and 15.4%. Studies have also shown that the timing of hydronephrosis is important. Early onset of hydronephrosis in fetal development is directly related to the prognosis.[1,4-10]

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PATHOPHYSIOLOGY

The ureter begins development as a solid cord of tissue that lengthens and canalizes during embryological development. The urogenital sinus undergoes differentiation to form the bladder and urethra at 10 weeks' gestation and 12 weeks' gestation, respectively. Current technology does not allow renal imaging before completion of nephrogenesis. After the fetus is formed, the placenta acts as a fetal hemodializer, maintaining salt, and water homeostasis. The fetal kidney begins to produce hypotonic urine between the 5th and 9th weeks of pregnancy.[11,12]

A deficiency at any point along the urinary tract after fetal kidney begins to function may present as ANH, causing temporary or permanent partial or complete obstruction of urine flow, and causing proximal expansion of the collection system. A deficiency at any point along the urinary tract after fetal kidney begins to function can lead to transient or permanent partial or complete obstruction of urine flow, causing proximal dilation of the collecting system that manifests as ANH. This obstructive process is mostly temporary and may not be pathological. However, if there is significant obstruction and is permanent, nephrogenic tissue may be affected, resulting in varying degrees of cystic dysplasia and renal failure.[13]

Most anomalies of the urinary tract detected during prenatal period are characterized by hydronephrosis or enlargement of the upper urinary tract due to their obstructive nature. Furthermore, ANH can be the result of non-obstructive processes, such as VUR, non-refluxing non-obstructed megaureter, and prune belly syndrome. Urine produced in the kidneys is the main component of amniotic fluid, which is necessary for normal lung development and prevention of compression deformities. Obstructive lesions, especially bilateral lesions, are harmful to the developing kidneys and lungs.[14,15]

Josephson reported that obstruction is associated with decreased renal blood flow, glomerular filtration, and potassium excretion, and only a small percentage of this damage is benefited by early intervention. Although there has not been much success in the current studies, we think that future studies will allow fetal surgical interventions to prevent obstruction in pathological ANH detected in the prenatal period.[16,17]

PRENATAL DIAGNOSIS AND FOLLOW-UP

Routine use of fetal US enables early detection of many intrauterine anomalies. Two methods are used to detect AHN. The first is the anteroposterior renal pelvic diameter (APRPD) measurement and the second is the grading system developed by the Society of Fetal Urology (SFU). SFU has developed a grading based on the US image of the long axis of the renal parenchyma and pelvicalyceal system [Tables 2 and 3].[18]

SFU grading system in AHN measurements is very valuable for an academic evaluation. However, the SFU grading system cannot be used much in practice in the detection of hydronephrosis in the intrauterine period due to its application and evaluation difficulties. For this reason, APRPD measurement is the most frequently used method and its value is high in practical application. Values with prognostic significance determined in the measurements made in the 2nd and 3rd trimesters of pregnancy using APRPD are shown in Table 2.[21,22]

AHN should be diagnosed using APRPD in the prenatal period and graded by the same method. APRPD, values that are 4 mm and above in the second trimester and 7 mm and above in the third trimester are considered abnormal and require postpartum evaluation. In cases with unilateral hydronephrosis, US should be performed once in the third trimester. In cases with bilateral hydronephrosis, US should be performed once a month until delivery, depending on the presence of symptoms suggestive of the lower urinary tract obstruction (progressive hydronephrosis, oligohydramnios, dilated, or thickened wall bladder) [Figure 1]. Diagnostic and therapeutic intervention in the

Table 1: Urinary system anomalies observed in pediatric hydronephrosis

• Ureteropelvic junction obstruction	• Primary non-obstructive megaureter
• Vesicoureteral reflux	• Megacalycosis
• Ureterovesical stricture	• Neurogenic bladder
• Urethral atresia	• Ectopic ureter
• Anterior urethral valve	• Ureterocele
• Fetal folds	• Posterior urethral valve
• Extrarenal pelvis	• Prune-belly syndrome
• Multicystic dysplastic kidney	• Tumors
• Peripelvic cysts	• Congenital urethral stricture

Table 2: AHN definition and staging according to APRPD measurement[19]

Classification of AHN	Second trimester APRPD (mm)	Third trimester APRPD (mm)	Postnatal (mm)
Mild	4–6	7–9	7–9
Moderate	7–10	10–15	9–15
Severe	>10	>15	>15

ANH: Antenatal hydronephrosis, APRPD: Anteroposterior renal pelvic diameter

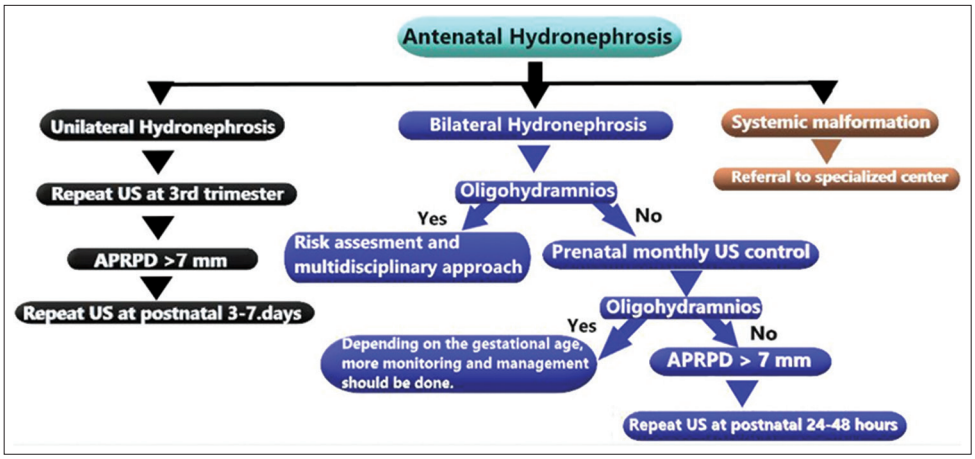

Figure 1: Prenatal antenatal hydronephrosis evaluation and management algorithm. APRPD: Anteroposterior renal pelvic diameter, US: Ultrasonography

prenatal period should only be considered in the presence of the lower urinary tract obstruction. If there is no life-threatening problem outside of the kidney in any AHN case after the 20th week of pregnancy, the pregnancy is not terminated. Infants with a high probability of detecting severe urological anomalies should be referred to a Pediatric Nephrology-Urology Center immediately after birth.[7,21-36]

POSTNATAL EVALUATION AND MANAGEMENT

Physical examination plays an important role in the evaluation of a baby with hydronephrosis. Undescended testis, association of anterior abdominal wall defects (Prune-Belly syndrome), presence of abdominal mass (ureteropelvic junction obstruction or multicystic dysplastic kidney), and palpation of the bladder (posterior urethral valve) are important findings.[3]

Figure 2 depicts the management of the follow-up and treatment of an infant with ANH.[21,22] The first step of ANH evaluation is urinary system US. Relative oliguria is seen in newborns at 24–72th h and hydronephrosis may not be observed in USG performed at this time. In patients with suspected posterior urethral valve, history of oligohydramnios, hydronephrosis of the solitary kidney, and bilateral severe hydronephrosis evaluation the first US should be performed within 24–48 h. In other patients, the first US should preferably be done within 3–7 days [Figure 2].[21,22] In the postnatal period, it is more appropriate to monitor infants with the SFU staging system, in which APRPD measurement, calyceal dilatation degree, and parenchymal involvement are evaluated in more detail [Table 3].[21] In addition, kidney echogenicity, ureter dilatation, and bladder wall problems should be evaluated.

Voiding cystourethrogram (VCUG) should be performed in cases with suspected bladder outlet obstruction and SFU Grade 3-4.[1] Hydronephrosis is defined as SFU ≥Grade 1 or APRPD ≥7 mm in a newborn baby. In babies with ARPRD <10 mm in the antenatal third trimester, Grade 1-2 hydronephrosis is usually detected in the postnatal period according to SFU. It is reported that hydronephrosis in these babies is probably not associated with obstruction, and the recovery rate is 98%.[34,35] Although it is not certain in cases with Grade 3-4 hydronephrosis or APRPD >12 mm according to SFU, it is likely to be a urological problem requiring surgical correction.[22,37]

US performed in the 1st week of life is insufficient to detect all abnormalities of the kidney and urinary system due to the low urine amount due to dehydration and low glomerular filtration rate. US performed in the 4th week is more sensitive and specific in detecting obstructive problems. Even if their first US is normal, all infants with AHN should be re-evaluated by US at the 4th week. The fact that these two USs performed in the first 4 weeks are normal is quite successful in excluding obstructive kidney diseases and severe dilated VUR. Patients with SFU Stage 0 and APRPD <7 mm as a result of US performed at the 4th week should not be considered as hydronephrosis and these cases need not be followed up.[21,29, 37]

Patients who are evaluated as unilateral or bilateral, isolated (without ureter enlargement, bladder problem, and kidney parenchyma problem) mild hydronephrosis (APRPD <10 mm or SFU Grade 1-2) in the first two US can be monitored only by US. The frequency of follow-up can be performed every 3–6 months, and then every 6–12 months, provided that it is evaluated according to the severity indicators of hydronephrosis. Most babies with mild hydronephrosis (SFU Stage 1-2, APRPD <10 mm) generally do not pose a significant problem for long-term follow-up. Hydronephrosis regresses spontaneously in the first 2 years of life in the

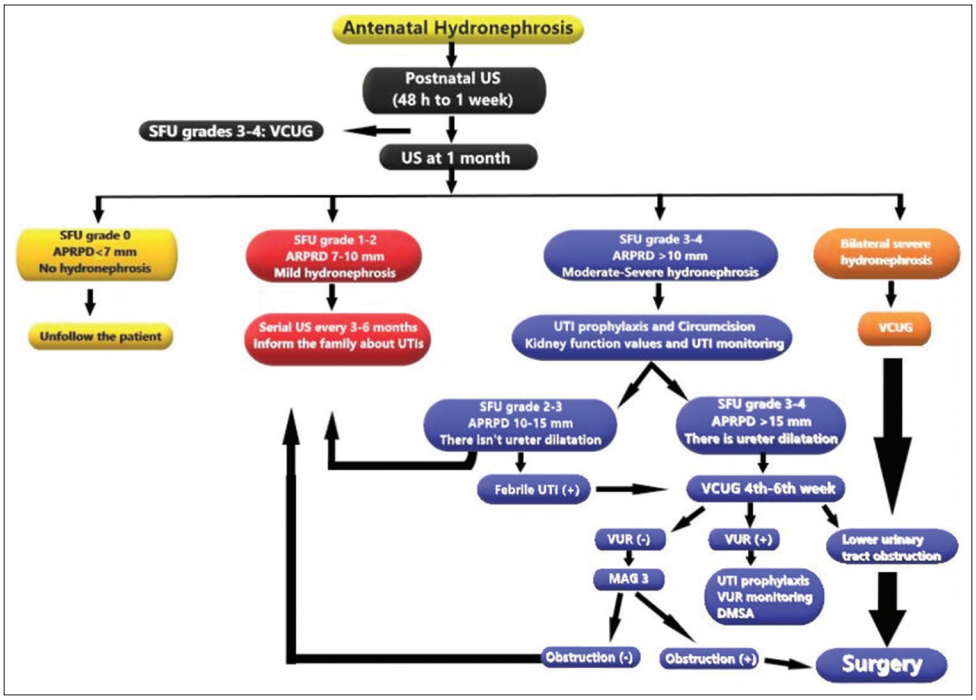

Figure 2: Postnatal AHN evaluation and management algorithm. APRPD: Anteroposterior renal pelvic diameter, MAG 3: 99mTc-mercaptoacetyltriglycine, SFU: Society of Fetal Urology, US: Ultrasonography, UTI: Urinary tract infection, VCUG: Voiding cystourethrogram

Table 3: Society of Fetal Urology grading system in antenatal hydronephrosis[20]

Grade	Figure	Central renal complex	Renal parenchyma thickness
0		Normal	Normal
I		Urine in pelvis barely splits sinus	Normal
II		Evident splitting of pelvis and major calyces	Normal
III		Wide splitting of pelvis, major and minor calyces	Normal
IV		Further splitting of pelvis, major and and minor calyces	Reduced

majority of patients, and non-US radiological examination or antibiotic prophylaxis is not required for these babies. Infants with moderate hydronephrosis with an APRPD of 10–15 mm can be followed up safely with US only, provided that the family is informed about urinary tract infection (UTI) and follow-up for UTI. Infants with APRPD >15 mm at baseline and SFU Stages 3-4 should be followed more closely. For these patients, it is extremely important to reveal the enlargement of the renal pelvis, calices, or ureters, or increased thinning of the cortical parenchyma. These patients should be imaged with VCUG between 4 and 6 weeks. According to the VCUG result, act as in the algorithm.[38-42]

VCUG INDICATIONS[43-45]

- Within 1–3 days of life in babies with signs of the lower urinary tract obstruction
- Infants with SFU Grades 3-4 on first postnatal US
- VCUG should be withdrawn after the urine becomes sterile in babies with AHN and febrile UTI during follow-up
- In USGs, VCUG should be withdrawn within 4–6 weeks in infants with APRPD> 15 mm, SFU Stage 3-4 or one of the criteria of ureter enlargement.

^{99M}TC-MERCAPTOACETYLTRIGLYCINE INDICATIONS

- Patients with moderate to severe hydronephrosis (APRPD> 10 mm and SFU Grade 3-4) but without VUR
- Regardless of the grade, patients with a dilated ureter, and no VUR should be evaluated with diuretic renography.

UTI AND CONTINUOUS ANTIBIOTIC PROPHYLAXIS

The families of all babies with AHN should be informed about the subjective UTI findings of this age group and the necessity of absolute routine urine analysis and correct urine culture test in cases with fever. Routine urinalysis and urine culture can be taken in infants and until the family becomes conscious, monthly/2-month periods. Afterward, when a UTI clinic is suspected or after a fever, a routine urinalysis should be performed. Urine culture should be done in case of nitrite and/or leukocyte esterase positive. Circumcision may be recommended for boys. The diagnosis of febrile UTI in the follow-up changes the follow-up plan in terms of VUR. Preventive antibiotic treatment should be initiated in patients with moderate to severe hydronephrosis (APRPD> 10 mm and SFU Grade 3-4) or dilated ureter until the diagnosis is completed or in patients with febrile UTI during the follow-up period and all patients with VUR.[8,22,46]

Trimethoprim-sulfamethoxazole should not be used as a prophylactic antibiotic in newborns, as it prevents the binding of bilirubin to albumin. Instead, oral amoxicillin should be started at a dose of 10 mg/kg/day as a single daily dose.

SURGICAL INTERVENTION INDICATIONS[22,43,47]

- Cases with VUR causing recurrent UTIs and developing new scar in renal parenchyma
- Infants with signs of lower urinary tract obstruction (progressive hydronephrosis, bilateral hydronephrosis, dilated or thickened-walled inadequate emptying bladder, and dilated posterior urethra)
- Cases who remained as 4th and 5th degree VUR at the end of the 1st year
- Cases with a radionuclide half-life ($t_{1/2}$)> 20 min in diuretic renography, not allowing flow and/or having differential kidney function lower than 40% on the side with obstruction
- Cases with posterior urethral valves should be performed early urethral catheterization, electrolyte abnormalities should be corrected and referred to pediatric urology centers for treatment of possible complications and surgical intervention
- Other indications for surgery are pain, palpable renal mass in the flank, and recurrent febrile UTIs.

CONCLUSION

When looking at the current studies in the literature, it was observed that there was no consensus on the evaluation and management of patients with AHN. In the light of the reviewed literature, AHN management algorithms were created according to the current data in the prenatal and postnatal period. The criteria for surgical treatment in AHN are still unclear. Thanks to the basic and clinical studies to be carried out in the future, the appropriate approach to these patients or the criteria to be selected for the cases to be operated will become clearer. Antibiotic prophylaxis and, if necessary, surgical intervention are vital for the follow-up of patients with AHN and to prevent renal failure with renal scarring after VUR.

REFERENCES

1. Woodward M, Frank D. Postnatal management of antenatalhydronephrosis. BJU Int 2002;89:149-56.
2. Roo R, Voskamp BJ, Kleinrouweler CE, Mol BW, Pajkrt E. Determination of threshold value for follow-up of isolated antenatal hydronephrosis detected in the second trimester. J Pediatr Urol 2017;13:594-601.
3. Ağras K. Diagnostic evaluation of infants with antenatal hydronephrosis. Turk J Urol 2011;37:47-53.

4. Liang CC, Cheng PJ, Lin CJ, Chen HW, Chao AS,Chang SD. Outcome of prenatally diagnosed fetalhydronephrosis. J Reprod Med 2002;47:27-32.
5. DiSandro MJ, Kogan BA. Neonatal management.Role for early intervention. Urol Clin North Am 1998;25:187-97.
6. Thomas DF. Fetal uropathy. Br J Urol 1990;66:225-31.
7. Sairam S, Al-Habib A, Sasson S, Thilaganathan B. Natural history of fetal hydronephrosis diagnosed on mid-trimester ultrasound. Ultrasound Obstet Gynecol 2001;17:191-6.
8. de Kort EH, Oetomo SB, Zegers SH. The long term outcome of antenatal hydronephrosis up to 15 millimetres justifies a noninvasive postnatal follow-up. Acta Paediatr 2008;97:708-13.
9. Passerotti CC, Kalish LA, Chow J, Passerotti AM, Recabal P, Cendron M, *et al*. The predictive value of the first postnatal ultrasound in children with antenatal hydronephrosis. J Pediatr Urol 2011;7:128-36.
10. Akıncı N, Kılıçaslan Ö. Outcomes of children with antenatal hydronephrosis admıtted to our polyclinic; the significance of pathological hydronephrosis and ımpact of severe antenatal hydronephrosis on prognosis. Duzce Med J 2016;18:60-5.
11. Elder JS. Antenatal hydronephrosis. Fetal and neonatal management. Pediatr Clin North Am 1997;44:1299-321.
12. Potter EL. Normal and Abnormal Development of the Kidney. Chicago: Yeer Book Medical Publishers; 1972.
13. Bernstein J. A classification of renal cysts. In: Gardner KD, editors. Cystic Diseases of the Kidney. New York: John Wilwy & Sons; 1976.
14. Chevalier RL, Chung KH, Smith CD, Ficenec M, Gomez RA. Renal apoptosis and clusterin follwing ureteral obstruction: The role of maturation. J Urol 1996;156:1474-9.
15. Chevalier RL,Gomez RA, Jones CE. Developmental determinants of recovery after relief of partial ureteral obstruction. Kidney Int 1998;33:775-81.
16. Josephson S. Suspected pyelo-ureteral junction obstruction in the fetüs: When to do what? II. Experimental viewpoints. Eur Urol 1991;19:132-8.
17. Coplen DE. Prenatal intervention for hydronephrosis. J Urol 1997;157:2270-7.
18. Odibo AO, Raab E, Elovitz M, Merrill JD, MaconesGA. Prenatal mild pyelectasis: Evaluating the thresholdsof renal pelvic diameter associated with normal postnatalrenal function. J Ultrasound Med 2004;23:513-7.
19. Walsh TJ, Hsieh S, Grady R, Mueller BA. Antenatal hydronephrosis and the risk of pyelonephritis hospitalization during the first year of life. Urology 2007;69:970-4.
20. Agunloye AM, Ayede AI, Omokhodion SI. The role of routine post-natal abdominalultrasound for newborns in a resource-poorsetting: A longitudinal study. BMC Pediatr 2011;11:64.
21. Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, *et al*. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 2010;6:212-31.
22. Aksu N, Yavaşcan O, Kangin M, Kara OD, Aydin Y, Erdoğan H, *et al*. Postnatal management of infants with antenatally detected hydronephrosis. Pediatr Nephrol 2005;20:1253-9.
23. Ek S, Lidefeldt KJ, Varricio L. Fetal hydronephrosis; prevalence, natural history and postnatal consequences in an unselected population. Acta Obstet Gynecol Scand 2007;86:1463-6.
24. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: A metaanalysis. Pediatrics 2006;118:586-93.
25. Sidhu G, Beyene J, Rosenblum ND. Outcome of isolated antenatal hydronephrosis: A systematic review and meta-analysis. Pediatr Nephrol 2006;21:218-24.
26. Maizels M, Wang E, Sabbagha RE, Dinsmoor M, Seshadri R, Ginsberg N, *et al*. Late second trimester assessment of pyelectasis (SERP) to predict pediatric urological outcome is improved by checking additional features. J Matern Fetal Neonatal Med 2006;19:295-303.
27. Kim HJ, Jung HJ, Lee HY, Lee YS, Im YJ, Hong CH, *et al*. Diagnostic value of anteroposterior diameter of fetal renal pelvis during second and third trimesters in predicting postnatal surgery among Korean population: Useful information for antenatal counseling. Urology 2012;79:1132-7.
28. Longpre M, Nguan A, Macneily AE, Afshar K. Prediction of the outcome of antenatally diagnosed hydronephrosis: A multivariable analysis. J Pediatr Urol 2012;8:135-9.
29. Ismaili K, Hall M, Donner C, Thomas D, Vermeylen D, Avni FE, *et al*. Results of systematic screening for minor degrees of fetal renal pelvis dilatation in an unselected population. Am J Obstet Gynecol 2003;188:242-6.
30. Feldman DM, DeCambre M, Kong E, Borgida A, Jamil M, McKenna P, *et al*. Evaluation and follow-up of fetal hydronephrosis. J Ultrasound Med 2001;20:1065-9.
31. Corteville JE, Gray DL, Crane JP. Congenital hydronephrosis: Correlation of fetal ultrasonographic findings with infant outcome. Am J Obstet Gynecol 1991;165:384-8.
32. Spitzer A. The current approach to the assessment of fetal renal function: Fact or fiction? Pediatr Nephrol 1996;10:230-5.
33. Ruano R, Duarte S, Bunduki V, Giron AM, Srougi M, Zugaib M. Fetal cystoscopy for severe lower urinary tract obstruction-initial experience of a single center. Prenat Diagn 2010;30:30-9.
34. Morris RK, Malin GL, Khan KS, Kilby MD. Systematic review of the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction. BJOG 2010;117:382-90.
35. Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Hemming K, Burke D, *et al*. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): A randomised trial. Lancet 2013;382:1496-506.
36. Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, *et al*. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol 2013;23:83-97.
37. Clautice-Engle T, Anderson NG, Allan RB, Abbott GD. Diagnosis of obstructivehydronephrosis in infants: Comparison sonograms performed 6 days and 6 weeks afterbirth. AJR Am J Roentgenol 1995;164:963-7.
38. Shukla AR, Cooper J, Patel RP, Carr MC, Canning DA, Zderic SA, *et al*. Prenatally detected primary megaureter: A role for extended followup. J Urol 2005;173:1353-6.
39. Matsui F, Shimada K, Matsumoto F, Takano S. Late recurrence of symptomatic hydronephrosis in patients with prenatally detected hydronephrosis and spontaneous improvement. J Urol 2008;180:322-5.
40. Gatti JM, Broecker BH, Scherz HC, Perez-Brayfield MR, Kirsch AJ. Antenatal hydronephrosis with postnatal resolution: How long are postnatal studies warranted? Urology 2001;57:1178.

41. Hafez AT, McLorie G, Bagli D, Khoury A. Analysis of trends on serial ultrasound for high grade neonatal hydronephrosis. J Urol 2002;168:1518-21.
42. Gökaslan F, Yalçınkaya F, Fitöz S, Özçakar ZB. Evaluation and outcome ofantenatal hydronephrosis: A prospective study. Ren Fail 2012;34:718-21.
43. Sinha A, Bagga A, Krishna A, Bajpai M, Srinivas M, Uppal R, Agarwal I. Revised guidelines on management of antenatal hydronephrosis. Indian J Nephrol 2013;23:83-97.
44. Anderson NG, Fischer J, Leighton D, Hector-Taylor J, McEwing RL. Management in children of mild postnatal renal dilatation but without vesicoureteral reflux. Pediatr Nephrol 2010;25:477-83.
45. Kangin M, Aksu N, Yavascan O, Anil M, Kara OD, Bal A, *et al*. Significance of postnatal follow-up of ınfants with vesicoureteral reflux having antenatal hydronephrosis. Iran J Pediatr 2010;20:427-34.
46. Kose E, Yavascan O, Turan O, Kangin M, Bal A, Alparslan C, *et al*. The effect of circumcision on the frequency of urinary tract infection, growth and nutrition status in infants with antenatal hydronephrosis. Ren Fail 2013;35:1365-9.
47. Gordon I, Piepsz A, Sixt R. Guidelines for standard and diuretic renogram in children. Eur J Nucl Med Mol Imaging 2011;38:1175-88.

How to cite this article: Engin MMN. Management of Infants Diagnosed with Antenatal Hydronephrosis and Determining the Need for Surgical Intervention. Clin J Surg 2020;3(2):1-7.