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EDUCATIONAL REVIEW

Management of antenatal hydronephrosis

Fatoş Yalçınkaya[1,2] · Z. Birsin Özçakar[1]

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Abstract

Antenatal hydronephrosis (AHN) is the most frequently detected abnormality by prenatal ultrasonography. Differential diagnosis of AHN includes a wide variety of congenital abnormalities of the kidney and urinary tract ranging from mild abnormalities such as transient or isolated AHN to more important ones as high-grade congenital vesicoureteral reflux or ureteropelvic junction obstruction. It is well known that the outcome depends on the underlying etiology. Various grading systems have been proposed for the classification of AHN on prenatal and postnatal ultrasonography. Mild isolated AHN represents up to 80% of cases, is considered to be benign, and majority of them resolve, stabilize, or improve during follow-up. Controversies exist regarding the diagnosis and management of some important and severe causes of AHN such as high-grade vesicoureteral reflux and ureteropelvic junction obstruction. Current approach is becoming increasingly conservative during diagnosis and follow-up of these patients with less imaging and close follow-up. However, there is still no consensus regarding the clinical significance, postnatal evaluation, and management of infants with AHN. The aim of this review is to discuss the controversies and provide an overview on the management of AHN.

Keywords Antenatal hydronephrosis · Ultrasonography · Ureteropelvic junction obstruction · Urinary tract infection · Vesicoureteral reflux

Introduction

Antenatal hydronephrosis (AHN), defined as dilation of renal pelvis and/or calyces, is the most frequently detected abnormality by prenatal ultrasonography (US) occurring in 0.5–1% of all pregnancies [1]. Although it is generally postulated as a marker of congenital abnormalities of the kidney and urinary tract (CAKUT), a specific disorder could not be identified in pretty good number of patients. However, it is well known that the outcome depends on the underlying etiology (Table 1), and CAKUT includes a spectrum of malformations that can occur at the level of the kidney, ureters, bladder, and/or urethra. On the other hand, more than half the cases of AHN resolve spontaneously by the end of gestation or during the first year of life [2]. Accordingly, differential diagnosis includes a wide variety of CAKUT ranging from mild abnormalities such as transient or isolated AHN to more important ones as high grade congenital vesicoureteral reflux (VUR) or ureteropelvic junction obstruction (UPJO). The underlying cause may also be a severe lower urinary tract obstruction (LUTO) such as posterior urethral valves (PUV) or prune-belly syndrome (PBS), requiring early diagnosis and urgent treatment. Despite the continuous advances in the understanding of the genetic basis and outcomes of CAKUT, there is still no consensus regarding the clinical significance, postnatal evaluation, and management of infants with AHN [3–5]. Consequently, the physician might have the risk of either subjecting infants who have no remarkable pathologies to significantly invasive examinations or neglecting an important anomaly by making fewer investigations. The aim of this review is to provide an overview on the management of AHN and to discuss the controversies about several common and important congenital abnormalities and issues that are related with this topic.

Prenatal evaluation

Ultrasonographic evaluation is routinely performed during pregnancy with an average of two scans for low-risk and four

✉ Fatoş Yalçınkaya
fyalcin@medicine.ankara.edu.tr

[1] Department of Pediatrics, Division of Pediatric Nephrology, Ankara University School of Medicine, Ankara, Turkey

[2] Çocuk Hastanesi, Çocuk Nefroloji B.D, Ankara Üniversitesi Tıp Fakültesi, Dikimevi, 06100 Ankara, Turkey

Table 1 Differential diagnosis of AHN

Transient AHN (resolves prenatally)
Isolated AHN (no renal abnormality)
Ureteropelvic junction obstruction
Vesicoureteric reflux
Ureterovesical junction obstruction
Multicystic dysplastic kidney
Duplex kidneys (± ureterocele)
Posterior urethral valves
Others: Ectopic ureter, megaureter, urethral atresia, urogenital sinus malformations, prune-belly syndrome, tumors

AHN antenatal hydronephrosis

scans for high-risk patients [6]. An anteroposterior renal pelvic diameter (APRPD) of ≤ 4 mm in the second and ≤ 7 mm during the third trimester are the most commonly accepted thresholds for prenatal US. At the beginning of 1990s, Society of Fetal Urology (SFU) reported a classification including mild, moderate, and severe AHN according to APRPD during the second and third trimesters (Table 2) [7]. Recently, Nyguen et al. suggested a multidisciplinary concensus on the classification of prenatal urinary tract (UT) dilation and evaluation of calyceal dilation, renal parenchymal thickness and appearance, bladder, and urethral abnormalities in addition to APRPD [6, 8].

It has been observed that prenatal UT dilation can resolve during pregnancy, remain stable, or may progress. The likelihood of resolution is related to the severity of the APRPD at initial diagnosis. Consequently, follow-up US during the third trimester in cases of moderate and severe AHN are recommended. Progressive UT dilation observed during pregnancy is usually associated with postnatal uropaties [9]. Several studies evaluated the outcome based on prenatal US findings. Coplen et al. [10] reported that when 15-mm renal pelvic dilation is used as a threshold, it correctly discriminates obstruction with sensitivity and specificity of 73% and 82%, respectively. Moreover, some authors revealed that the larger the APRPD, the more likely it is to be caused by obstructive uropathies and the lower the spontaneous resolution rate [10–12]. Additionally, a meta-analysis of the literature found

Table 2 SFU classification system [7]

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

SFU, Society of Fetal Urology; *AHN*, antenatal hydronephrosis; *APRPD*, anteroposterior renal pelvic diameter

that the severity of UT dilation based on the SFU criteria correlated with urological pathologies, except for VUR [13]. Nevertheless, it should be noted that these surveys varied widely, applying different gestational age ranges, having different APRPD cut-offs, and outcomes. Although prenatal ultrasonography frequently reveals isolated hydronephrosis, it should be kept in mind that it can be associated with ureteral, bladder, and amniotic fluid abnormalities. Therefore, prenatal US especially at 16–20-week gestation should include evaluation for lower urinary tract obstruction, renal dysplasia, and extra-renal structural malformations. An algorithmic approach for the prenatal evaluation and management of AHN is shown in Fig. 1. According to this approach, if the patient has unilateral AHN without any malformations in the second trimester, US should be repeated at the third trimester; and if APRPD is more than 15 mm, postnatal US should be performed at 3–7 days of life. If AHN is mild (7–9 mm) or moderate (9–15 mm) at the third trimester, it is better to perform postnatal US after 7 days of life. If the APRPD is less than 7 mm, routine postnatal evaluation with US at 3 to 6 months of age is adequate [14].

If there is bilateral AHN, the most important question is whether there is oligohydramnios or not. If there is no oligohydramnios, the clinician should perform serial USs every 2 to 6 weeks upon the situation. Gestational age at appearance of oligohydramnios showed excellent accuracy in predicting the risk of perinatal mortality with an optimal cut-off at 26-week gestation. Fetuses with normal amniotic fluid volume at 26-week gestation presented with low risk of poor outcome and were therefore defined as cases with mild LUTO. In fetuses referred before the 26th week of gestation, the urinary bladder volume (BV) was the best unique predictor of perinatal mortality. A BV of 5.4 cm^3 and appearance of oligohydramnios at 20 weeks were identified as the best threshold for predicting an adverse outcome. Lower urinary tract obstruction cases with a BV ≥ 5.4 cm^3 or abnormal AF volume before 20-week gestation were defined as severe and those with BV < 5.4 cm^3 and normal AF volume at the 20-week scan were defined as moderate. Risk of perinatal mortality significantly increased according to the stage of severity, from mild to moderate to severe stage, from 9 to 26 to 55%, respectively. Similarly, risk of severely impaired renal function increased from 11 to 31 to 44%, for mild, moderate, and severe LUTO, respectively [15].

In utero management, options for LUTO are limited. Insertion of vesicoamniotic shunt (VAS), surgical ablation of valves, or serial amnioinfusions is offered. Although some of these procedures have been demonstrated to increase perinatal survival, none of them could prevent renal damage. Moreover, these interventions might be related with serious complications including intrauterine fetal demise or premature delivery [16, 17]. Morris et al. [18] reported a large, multicenter, randomized study to assess the effectiveness of VAS and found

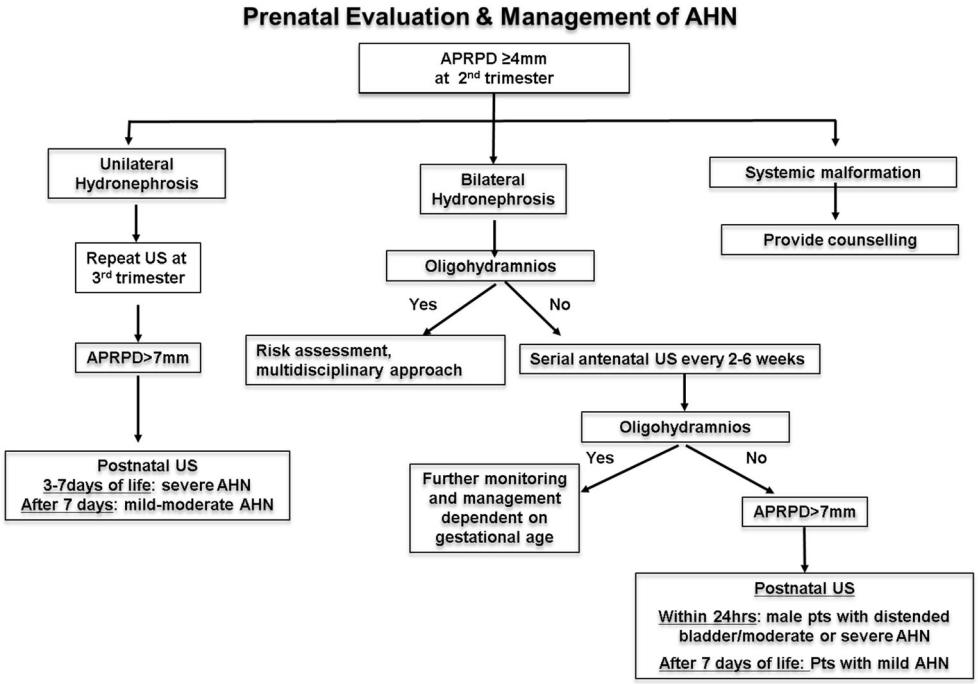

Fig. 1 Prenatal evaluation of antenatal hydronephrosis (AHN)

that survival seemed to be higher in the fetuses receiving this therapy. However, they suggest that the chance of newborn babies surviving with normal renal function is very low irrespective of whether or not VAS is done. A recently published updated systematic review and meta-analysis showed an advantage for perinatal survival in fetuses treated with VAS compared with conservative management. Nevertheless, 1–2 year survival and outcome of renal function after VAS procedure remain uncertain [19]. On the other hand serial amnioinfusions were performed in only a few cases and found effective [20, 21]. Thus, we suggest that in utero management of LUTO can be offered in selected cases in experienced centers taking the risks of complications and inconclusive results.

Postnatal evaluation

Postnatal US of the kidney, urinary tract, and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. This is a noninvasive procedure which provides reliable information regarding kidney structure, size, parenchyma (enhanced echogenicity, presence of cortical cysts), collecting system dilation, and lower urinary tract abnormalities.

Numerous grading systems have been proposed for the classification of AHN on postnatal US. In 1978, Ellenbogen et al. [22] proposed a descriptive grading system which assesses renal pelvicalyceal dilation and parenchymal thickness, categorizing AHN as mild, moderate, or severe. Whereas, the semi-quantitative grading system of SFU for postnatal hydronephrosis is based on US findings of the degree of renal-pelvic and calyceal dilation and takes into account the integrity of the parenchyma within four grades of increasing severity [7]. These are still the two most commonly used grading systems for the postnatal evaluation of AHN. Some detailed and complicated multidisciplinary classification systems which included a wide range of US parameters for the classification of postnatal urinary tract dilation have recently been reported [6, 8, 9]. However, the usage of these systems in routine clinical practice needs validation in large patient populations and training for both radiologists and clinicians.

Although progressive dilation observed during pregnancy is more often associated with CAKUT, occasionally prenatal US findings are not available for the physicians in current clinical practice. Generally, it is only mentioned by parents that there is a history of prenatal kidney problems, without any additional details characterizing the extent and severity of the problem. All patients with AHN should be evaluated by an ultrasound postnatally. In recent years, SFU grades 1 or 2 or postnatal APRDP < 20 mm are regarded as low risk whereas children with SFU grade 3 or bilateral HN or postnatal APRPDs 20–30 mm are mentioned as intermediate risk. Patients with SFU grade 4 HN or postnatal APRPDs > 30 mm are graded as high risk and both independently predicted lower likelihood of resolution [23]. If there is a suspicion of bladder outlet obstruction with bilateral hydro-uretero-nephrosis with a thick-walled distended bladder in a male infant, immediate postnatal US and instillation of a catheter is required for early and urgent postnatal diagnosis and treatment LUTO such as PUV.

An initial normal postnatal US in children with AHN may be misleading. Aksu et al. [24] observed that 45% of the children with an initial normal first postnatal scan had an

abnormal US at follow-up. In another study, 5% of the patients requiring surgery for obstructive uropathies had a normal US at the first week of gestation but an abnormal scan at 1 month of age [25]. Therefore, in children with AHN, a second postnatal US should be performed even if the first one is normal. The ideal time for the first US is after the fifth or seventh day of life and the second is recommended at 4–6 weeks of age [6, 23–25].

In the last years efforts for the evaluation of substances that could be utilized as potential biomarkers in children with AHN, especially in UPJO, to predict risk of obstruction and renal functional impairment have emerged. These included epidermal growth factor (EGF), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemotactic peptide (MCP-1), transforming growth factor β1 (TGFβ1), and osteopontin (OPN). However, wide range of results reported in different studies due to the heterogeneity of the age groups, duration of follow-up, different control groups, and sampling location (pelvis or bladder). It seems that biomarkers may have a crucial role to help stratify the risk of obstruction and renal injury in infants with high-grade hydronephrosis. In the meantime, the optimal role of either a single biomarker or a panel of biomarkers in the clinical evaluation has yet to be established [26, 27]. In 2006, Decramer et al. [28] identified urinary polypeptides that enabled the severity of UPJO and validated these biomarkers in a prospective blinded study. They showed that using these non-invasive biomarkers, they were able to predict the clinical evaluation of neonates with UPJO. Recently, in a pilot study, urinary carbohydrate antigen 19-9 (CA19-9) levels were found to be significantly higher in the urine of pregnant women carrying fetuses with severe AHN as compared to controls and suggested as a non-invasive biomarker for the diagnosis of AHN [29]. We think that biomarkers will have an effective role in the follow-up of patients with AHN in the near future.

Mild isolated antenatal hydronephrosis

Mild isolated AHN was defined by an APRPD of 7–10 mm diagnosed by fetal US in the third trimester of gestation and persistent postnatal mild hydronephrosis. This group represents up to 80% of cases and is considered to be more benign than those of moderate or severe grades [30]. A review of the literature indicates the risk of urological pathology with mild isolated AHN to be 12%, compared to 45% and 88% for the moderate and severe cases, respectively [13]. In addition, 70–98% of this group resolve, stabilize, or improve during follow-up. A recent study showed that the risk of VUR and UTI is 3% each, and only 2% of children with mild AHN eventually required surgical intervention [30].

Although there is sufficient evidence that mild AHN is a self-limited condition, a small number of patients (2–10%) might have significant urological pathologies and develop complications such as febrile urinary tract infection, hypertension, and renal injury if not recognized and not regularly followed up. Furthermore, it is widely known that not all cases of PUV present with a severe UT dilation. Therefore, mild AHN does not necessarily exclude the diagnosis of PUV [9, 31, 32]. Accordingly, SFU recommends at least 1 year of follow-up for mild AHN while others propose that they should be followed with US yearly or every 2 years, until they are mature enough to verbalize signs of flank pain or dysuria to identify the few patients who may have clinically significant urological pathologies [9, 30]. Thus, even recommendations regarding the evaluation and management of mild AHN vary from no follow-up to extensive postnatal radiological evaluation including voiding cystourethrography (VCUG), renal nuclear scintigraphy (RNSc), and medical therapies such as continuous antibiotic prophylaxis (CAP) [13, 30, 33–35]. A recent survey on the management of mild AHN including pediatric radiologists, pediatric urologists, and maternal-fetal obstetricians has shown a lack of consensus [36]. In our opinion, it seems reasonable to follow up carefully patients with mild AHN without major investigations.

Ureteropelvic junction obstruction

Ureteropelvic junction obstruction is typically represented by severe hydronephrosis on postnatal imaging and underrepresented in patients with mild (8%) or moderate (23%) hydronephrosis. So, the degree of postnatal hydronephrosis is predictive for the presence of UPJO. Although the management of UPJO was traditionally accepted as surgical, spontaneous resolution overtime has been demonstrated [37]. However, the ability to define which children will resolve their condition or will benefit from a surgical procedure remains elusive [38, 39]. Length of APRPD and preoperative differential renal function (DRF) on diuretic renal scintigraphy (DRSc) were found to be the only independent predictors for the need for surgery [40]. DRSc with 99Tc MAG-3 is the most commonly used modality to determine the presence of unilateral upper urinary tract obstruction in infants with AHN beginning from 6 to 8 weeks of age. This imaging technique allows differentiation between non-obstructive and obstructive hydronephrosis and estimates DRF. A DRF of less than 40% and/or decreased DRF of more than 10% on serial diuretic renograms show obstructive pattern [41]. Even some authors recommended immediate pyeloplasty in patients with decreased DRF and delayed tissue transit time [42]. However, this is also a controversial topic because there are several pitfalls and difficulties in the interpretation of renography for the evaluation of upper urinary tract obstruction in infants. Duong and his colleagues [43] from Belgium reported a well-designed study by comparing US parameters with DRSc results for the prediction of the patient in whom DRSc is redundant. Interestingly, the results of this

retrospective study showed that an APRPD < 30 mm, a calyceal dilatation of < 10 mm, and a normal parenchymal thickness (which could be found in ref. [44]) were associated with a low probability of decreased renal function or poor renal drainage. In other words, they suggested that DRSc should only be performed in patients with APRPD more than 30 mm, major calyceal dilatation (> 10 mm), and/or parenchymal thinning [43]. Thus, it seems logical to follow patients with APRPD 20–30 mm carefully and order DRSc and urological consultation to the patients with APRPD > 30 mm.

Current approach is becoming increasingly conservative with respect to operative intervention in the majority of patients with UPJO [45]. Recommendations for the management of asymptomatic infants with unilateral UPJO nowadays included discussions of individual patients at nephro-uroradiology meetings in order to reach a consensus using the initial ultrasound scan and DRSc results unless there is gross AHN. Those who are managed conservatively should regularly be followed with US. Repeated DRSc should come up when the patient becomes symptomatic or if the US suggests increasing pelvic dilation and/or cortical thinning. During the last years, a risk-stratified approach towards less imaging in children with unilateral UPJO was even suggested [46]. It was demonstrated that if patients are monitored closely, deterioration in renal function can be recovered by prompt pyeloplasty [47]. On the contrary, some authors emphasize to find out new realistic estimates of nonsurgical management of unilateral UPJO [39].

Vesicoureteral reflux

The frequency of VUR in healthy children is 1–2% [48]. The incidence ranges from 8 to 38% in infants with a history of AHN [13, 49]. When AHN is continued on the postnatal US, approximately 40% of the children have VUR whereas when two postnatal US evaluations are normal, only 7% of the infants have VUR and if present is likely low grade [35]. Notably, VUR is the only uropathy in which the degree of UT dilation observed on the prenatal and postnatal US does not correlate with increasing risk of pathology. Moreover, there is poor correlation between grade of VUR and severity of AHN. Increased incidence of VUR among different grades of AHN has been previously reported in the literature, suggesting the importance of investigation of this pathology even in mild cases [13, 50]. In contrast, other studies suggested that VCUG is not mandatory in children with AHN of grade 2 or less [33]. An interesting retrospective study was published from Boston Children's Hospital that includes more than 500 children with mild isolated AHN. Vesicoureteral reflux was identified in only 1.7% of the study group. In addition, four of the 23 children with mild AHN and a urinary tract infection (UTI) developed this infection after having a VCUG. Consequently, the authors propose that routine performance of VCUG for mild AHN is not necessary, but it should be performed for patients who have febrile or recurrent UTI during follow-up. This recommendation would avoid unnecessary radiation exposure, discomfort, and risk of UTI in children with mild AHN [30]. On the other hand, VCUG is still absolutely indicated as an immediate postnatal study for neonates with suspected bladder outlet obstruction. In addition, the presence of cortical abnormalities on US, bilateral high-grade hydronephrosis, ureterocele, abnormal bladder, and hydroureter are other indications for performance of VCUG in various studies [32, 51, 52]. The use of VCUG to detect reflux has been reported to be optional in all other conditions. In fact, some studies have even proposed criteria for the well tolerated omission of VCUG in many situations reported previously during postnatal management [26, 53]. Despite all these debates, it should be kept in mind that conventional VCUG remains the gold standard because the test allows better determination of the grade of VUR and provides precise anatomic detail of bladder and urethra as compared to US and radionuclide scintigraphy. Accordingly, controversies exist regarding the diagnosis and management of VUR which raise the question as to the utility of diagnostic evaluation for VUR in infants with AHN. In our opinion, careful monitoring with US avoids unnecessary invasive and irradiating examinations, and recurrent febrile UTI is the main indication of VCUG for the patients with AHN.

Urinary tract infection and continuous antibiotic prophylaxis

The frequency of UTI in patients with asymptomatic AHN ranges from 1 to 29%, being as low as 2–5% in low grade whereas it is higher (15–29%) in the patients with SFU grades 3–4 [54]. Moreover, the risk of pyelonephritic episodes in patients with AHN is highly dependent on age, gender, the level of urinary outflow disturbance, and severity of obstruction; thus, it is hard to suggest a general approach for CAP [55–57]. However, majority of the patients have mild isolated AHN and they do not need CAP. On the other hand, consideration of CAP comes up mostly in the patients with recurrent febrile UTI and the suspicion of VUR or severe obstruction.

In patients with AHN and VUR, the frequency of UTI has been reported in a very wide range between 1 and 52% that suggests confusion in this group of patients [50, 58, 59]. On the other hand, recurrent UTI incidence in children with primary VUR presenting symptomatically is well documented. The patients with low-grade reflux were found to have a similar risk of recurrent UTI to those without VUR whereas the incidence of further UTI in those with high-grade VUR detected after a symptomatic presentation is higher [54, 59–61]. Nevertheless, the risk of UTI in asymptomatic primary VUR diagnosed just for the investigation of AHN is less clear.

VUR can resolve spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in grades I–II and 30–50% in grades III–V VUR within 4–5 years of follow-up [62]. The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [63, 64]. Renal scarring occurs in approximately 10% of AHN patients whereas, in patients with LUTD, this figure may rise to 30% [13, 50, 65]. Scarring in the kidney may adversely affect renal growth and function, with bilateral scarring increasing the risk of renal insufficiency and is the most common cause of childhood hypertension [48, 50]. It is suggested that there is a correlation between the febrile UTI's and the risk of new scarring. Several important studies show that CAP is associated with a reduction in the risk for recurrent UTIs and several physicians still favor starting antibiotic prophylaxis for all neonates and infants with VUR as the conventional initial management [66, 67]. Generally, cotrimoxozole or nitrofurantion are used in UTI prophylaxis in children. In infants less than 2 months of age, amoxicillin or cephalosporins are recommended. Serious side effects of these drugs are extremely rare [68–70]. However, in the long term, CAP could increase the risk of multidrug resistant infections [71]. Recently, it was reported that CAP was also correlated with increase in body mass index [72]. Circumcision during early infancy and close follow-up with general evaluation, growth and blood pressure monitorization, and performance of relatively noninvasive imaging studies may be considered parts of the conservative approach to monitor kidney status [73–76]. However, the evidence on the usage of antibiotics to prevent recurrent symptomatic UTI was found to be not strong as it was expected [77, 78]. Due to the studies showing association of CAP with increased risk of resistant infections [79], in recent years, strong opinion emerged in favor of close follow-up with simple observation of these children even without CAP. We believe that an ongoing prospective multicenter European study regarding prophylaxis in congenital VUR will clarify majority of questions about this issue.

Conclusion

There is still no consensus for the evaluation and management of the patients with AHN that represents a heterogeneous group with different diseases having different outcomes. According to the results of the studies done so far, it is not possible to make a really true and useful algorithmic approach for the evaluation and management of the patients who might have various causes of AHN. So, we still need properly randomized, double-blinded prospective studies, that include patients with AHN stratified according to different types of CAKUT to have truly accurate and beneficial outcomes for the patients.

Key summary points

- Antenatal hydronephrosis is the most frequently detected abnormality by prenatal US and its outcome depends on the underlying etiology.
- There is still no consensus for the evaluation and management of patients with AHN.
- Mild isolated AHN represents up to 80% of the cases and generally regarded as a self-limited condition.
- Conservative approach with careful close follow up for patients with asymptomatic VUR and UPJO is generally recommended in recent years.

Questions (answers are provided following the reference list):

1. What are the most frequently accepted APRPD thresholds for prenatal diagnosis of AHN?

   a) ≤ 4 mm in the second and ≤ 10 mm in the third trimester
   b) ≤ 4 mm in the second and ≤ 7 mm in the third trimester
   c) ≤ 5 mm in the second and ≤ 10 mm in the third trimester
   d) ≤ 7 mm in the second and ≤ 12 mm in the third trimester

2. What is the optimal time for postnatal US in a male patient with bilateral moderate hydronephrosis and distended bladder?

   a) Within 24 h
   b) Within 48 h
   c) 3–7 days of life
   d) After 7 days of life

3. Which one of the following is wrong about mild isolated AHN?

   a) Defined as an APRPD of 7–10 mm diagnosed by fetal US in the third trimester of gestation.
   b) Majority of them resolve, stabilize, or improve.
   c) A substantial number of patients in this group require surgical intervention.
   d) Mild AHN does not necessarily exclude the diagnosis of PUV.

4. Which one of the following is wrong about VUR and UPJO?

   a) The correlation between the severity of AHN and grade of VUR is poor.
   b) The degree of postnatal hydronephrosis is predictive for the presence of UPJO.

c) Length of APRPD and preoperative DRF on DRSc were found to be predictors for surgery.
d) DRSc with 99Tc MAG-3 is indicated as an immediate postnatal study for neonates with suspected bladder outlet obstruction.

5. What should be recommended to a patient with AHN who had a normal postnatal US which is performed in the 5th day of life?

a) No need to perform any other investigation
b) A second US should be performed at 4–6 weeks of age
c) A second US should be performed at 1 year of age
d) Perform US every 3 months in the first year

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Answers

1. b; 2. a; 3. c; 4. d; 5. b