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Ultrasonography contribution in detection of Reno-urinary anomalies: a cohort study

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Abstract

Aims: The current study aims to assess the role of ultrasound (US) parameters in explaining the variance of hydronephrosis grades in reno-urinary anomalies, as well as their performance in quantifying the incidence of patients with uropathies. **Methods:** In this study 196 patients were prospectively included. All of them had renal/urinary tract anomalies and were recruited from 5992 US examined hospitalized patients. Fifty patients were referred also to renal 99mTc- DMSA or 99mTc-DTPA scintigraphy. The diagnostic performance of renal ultrasound and scintigrafy parameters was assessed. **Results:** Pelvis antero-posterior diameter (APD) values were strongly correlated with other investigated parameters. They correlated with measurements of US parenchyma values (r=0.59, p=0.001), pelvis area (r=0.76, p=0.001) and with scintigraphy long axis measurements (r=0.89, p=0.001). In multiple regression analysis, the pelvis APD is the only independent predictor of high grades hydronephrosis (p=0.001) and explained 62.4% of the variance of hydronephrosis grades. The cut-off values for detection of significant hydronephrosis (grades 3,4) was 11 mm or more, and for detection of severe, in need of surgery, hydronephrosis was 19 mm or more. **Conclusions:** The diagnostic performance of ultrasound was good, similar to those previously published by other authors. US detected pelvis APD is the main predictor for high grades hydronephrosis but other parameters also influence the uropathy grades.

Key words: reno-urinary anomalies, ultrasound, scintigraphy, diagnostic performance

Rezumat

Scopul lucrării este de a evidenția capacitatea ultrasonografiei (US) în detectarea incidenței anomaliilor renale şi de a stabili acuratețea diagnostică a parametrilor ultrasonografici în diagnosticul acestora. **Material si metoda:** S-a efectuat un studiu prospectiv în care au fost selectați 196 pacienți cu anomalii renourinare dintr-un lot de 5992 de pacienți evaluati în cadrul Departamentului de Ultrasonografie al Clinicii Pediatrie III, Cluj- Napoca, România. Din cei 196 de pacienți studiați, 50 au efectuat scintigrafie renală cu DMSA/DTPA. S-a evaluat performanța diagnostică a parametrilor ultrasonografici şi scintigrafici. **Rezultate:** Valorile medii ale diametrului antero- posterior al pelvisului (DAP) s-au corelat semnificativ cu valorile ultrasonografice al parenchimului renal (r=0.59, p=0.001), cu aria pelvisului renal (0.76, p=0.001) şi cu valorile scintigrafice ale axului lung renal (r=0.89, p=0.001). Efectuand analiza multivariată prin regresie multiplă, DAP este singurul parametru predictiv, semnificativ din punct de vedere statistic, pentru hidronefroza severă. Acesta explică 62.4 % din variabilitatea gradelor de hidronefroză la pacientii cu anomalii renale. Valorile prag semnificative ale DAP pentru detectarea hidronefrozei severe (grad 3,4) şi a celei care necesită tratament chirurgical au fost 11 mm respectiv 19 mm. **In concluzie,** ultrasonografia demonstreaza o performanța diagnostică bună, similară cu cea raportată în literatura de specialitate. Determinarea DAP al pelvisului renal este singurul indicator semnificativ din punct de vedere statistic pentru hidronefroza severă, însă în viitor trebuie luat in considerare şi aportul altor parametri ultrasonografici.

Cuvinte cheie: malformații renourinare, ecografie, scintigrafie, performantă diagnostică

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Introduction

Congenital anomalies of the kidneys and urinary tract have rapidly gained popularity in recent years. A major challenge of these conditions is that they can occur not only prenatally**,** but also in childhood or adulthood. Antenatal detected hydronephrosis can represent a predictor of a various number of renal pathologies, such as uretero-

pelvic junction obstruction (UPJO), vesico-ureteral reflux (VUR), posterior urethral valves (PUV) and vesico-ureteral junction obstruction (VUJO) [1].

There are different techniques used for the diagnostic purpose of these malformations. The search for the best technique is focused on early detection in order to prevent irreversible damage of the renal parenchyma. This search has resulted in the production of various algorithms for follow-up and management of antenatal detected hydronephrosis [2,3]. The postnatal investigation of hydronephrosis usually includes ultrasound (US) scans, voiding cystourethrography (VCUG) and renal scintigraphy [4]. There is a consensus among clinicians that US must be the initial postnatal study for the evaluation of foetal hydronephrosis [1,5,6] . Being one of the most common birth defects, US detected renal pelvis dilatation (RPD) occurs in approximately 1% of foetuses [7,8,9].

Our study was designed primarily to observe the role of ultrasound in detecting infants with renal anomalies and to quantify the accuracy power of US in evaluating and follow up of this pathology. We discuss the possibility of standardizing postnatal ultrasonographic markers predictive of significant uropathies that may avoid wide fluctuations in response time for optimal treatment and reduce an undesirable outcome.

Patients and methods

We obtained written informed consent and the approval of the Paediatric Hospital Ethics Committee. A cohort study was performed in a prospective manner on 196 children with renal/urinary tract anomalies recruited from 5992 US examined patients hospitalized in Cluj-Napoca IIIrd Paediatric Clinic, Romania, from August 2007 to February 2010.

Patients' demographic characteristics were assessed with a written questionnaire. With parents' approval, all the children investigated were searched for potential prenatal detection of reno-urinary abnormalities. We included infants having ultrasound pre/postnatal detected renal anomalies such as agenesis or dysplasia, renal ectopia/malposition, horseshoe kidneys and patients having urinary tract anomalies such as mild hydronephrosis, severe hydronephrosis due to uretero-pelvic junction obstruction, primary megaurether, vesico-ureteral reflux, ureteral duplex system associated or not with ureterocele, uretral obstruction, such as posterior uretral valves, and other reno-urinary anomalies, such as vesico-ureteral junction obstruction or multicystic dysplastic kidney. Special attention was paid to those having renal pelvis dilatation. We excluded from the statistical analysis infants with antenatal detected anomalies with no postnatal diagnostic or follow up.

Two-dimensional postnatal US evaluation was performed using age adapted multifrequency transducers (3-9 MHz). The patients were well hydrated, examined in prone position and with a full bladder. For patients having renal anomalies, kidneys were assessed for shape, size and location. For patients with urinary tract anomalies each kidney's size, parenchyma thickness, renal pelvis AP diameter and area, if visible, were assessed. Only renal units with anomalies were included in the study design. Based on the classification of the Society for Foetal Urology, we used a paediatric adapted scale for grading hydronephrosis, as follows: grades 1, renal pelvis that is just visible, with an AP diameter over 5mm but not greater than 10 mm; grade 2, some visible normal – shaped calyces; grade 3, marked dilatation of renal pelvis and calyces, with loss of normal calyceal shape (without parenchyma narrowing) and grade 4, important dilatation of the entire collecting system with additional parenchyma narrowing [10].

For following up patients with pelvic dilatation, further diagnostic procedures were considered. If regression occurred, the child was no longer followed up. If isolated unchanged low grade hydronephrosis was detected, US follow up was performed. In cases of high grade hydronephrosis or progression, ureteral dilatation, parenchyma narrowing or repeated urinary tract infections, other investigations were added – voiding cystouretrography or renal scintygraphy. ^{99m}Tc- DMSA and ^{99m}Tc-DTPA diuretic scintigraphy was conducted by a senior nuclear medicine specialist, and relative renal size and split function were assessed and reported. Sedation was administered to 18 patients as per department protocol for DMSA/DTPA scanning. To assess the need for surgery we used the following criteria: alteration of the renal function, progression of hydronephrosis, high degree hydronephrosis, symptomatic hydronephrosis.

Statistical analysis was performed using MedCalc for Windows, version 9.3.2.0 (MedCalc Software, Mariakerke, Belgium). Data in text and tables are reported as mean (95% IC) or percentage (%). Demographic variables were assessed using descriptive statistics. Differences in mean values were tested by one-way analysis of variance (ANOVA); relationships between the parameters were characterized using the Spearman correlation coefficients. The agreement between US and scintigraphy was inspected through the two-way mixed interclass correlation coefficient (ICC) [11]. The diagnostic performance of AP diameter was assessed using sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LR)

and receiver operating characteristic (ROC) curves. A p value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 196 children (117, 59.7% males) were included in the analysis. The first ultrasound examination was conducted at the mean age of 28.9 (26.17 - 31.74) months. From all patients, 73 (1.21%) had antenatal diagnosis with postnatal follow up. The mean follow up time was 26 (1.32 - 32.81) months for 130 patients and 66 infants (33.7%) were evaluated in one examination. Thirty – one patients (15.81%) presented with renal anomalies. The percentage of patients assessed as having urinary tract malformations was 84.29% (165 infants). Of the 196 patients included in the study, 50 patients (25.51%) presented with persistent significant uropathy and underwent renal scintigraphy, as shown in table I. There was a predominance of uretero-pelvic junction obstruction (n=20, 40%) among patients performing DTPA scintigraphy. Eighteen patients, (36%) of those having high grade hydronephrosis, fulfilled the criteria for surgical treatment.

Baseline ultrasound and scintigraphy characteristics of patients with renal tract abnormalities undergoing renal scintigraphy are summarized in Table II. Children with nonobstructive hydronephrosis were part of an early diagnosis, at a mean age of 28.7 (22.4 – 79.9) years, followed at close range by patients with uretero- pelvic junction obstruction, with a significant difference from those with vesico-ureteral reflux. We found no significant differences between US measurements and those performed using renal scintigraphy. There was a significant difference in mean (95% CI) pelvis area at postnatal US scan between vesico-ureteral reflux, primary megaureter and uretero-pelvic junction obstruction. The split renal function did not differ between the pathologies studied. We found 11 renal units with parenchyma damage detected by DMSA scintigraphy in patients having vesico-ureteral reflux.

Table I. Postnatal diagnosis of renal/urinay tract anomalies.

	Patients (n=196)	**Scintigraphy n(%) DTPA/ DMSA* (n=50)**
Renal anomalies n(%)	31 (15,81)	3 (6)
Agenesis/hypoplasia	16 (8,1)	1(2)
Ectopia	7(3,6)	1(2)
Horseshoe kidney	8 (4,1)	1(2)
Urinary tract anomalies n(%)	165 (84,29)	47 (94)
Nonobstructive HN	59(30,1)	6 (12)
UPJO	23(11,7)	20 (40)
Primary megaurether	26(13,2)	4 (8)
Vesico-ureteral reflux	26(13,2)	12 (24)
Ureteral duplex system	14(7,2)	2 (4)
Posterior uretral valves	2(1,2)	-
Other	15(7,6)	3 (6)
HN in need for surgery (n,%)	18 (9.18)	18 (36)

*Patients suspected of having vesico-ureteral reflux

Table II. Baseline characteristics of patients with renal tract anomalies undergoing renal scintigraphy.

	Scintigraphy diagnosis				
Parameters†	**Nonobstructive hydronephrosis** (6 Renal Units)	**Primary megaureter** (6 Renal units)	**Vesico-ureteral reflux** (17 Renal units)	**UPJO** (29 renal units)	**p**
Age (months)	28.7 (22.4 – 79.9)	38 (10.1 - 65.9)	53.7 (26.9 - 80.5)	34 (16.8 - 51.1)	0.01
Mild HN‡(n,%)	6 (10.34)	5(8.6)	9 (15.5)	11 (18.96)	
Severe HN‡n, %)	-	1 (1.72)	8 (13.79)	18 (31.03)	0.03
Scintygraphic long axis (mm)	73.7 (50.8 – 96.6)	75.1 (59.8 - 90.5)	69.2 (60.6 - 77.9)	76.2 (70.2 - 82.1)	Ns* Ns
US long axis(mm)	71 (49.1 – 92.9)	76.5 (61.8 – 91.1)	70.1 (59.9 – 80.1)	76.2 (68.1 – 84.3)	Ns
Paremchyma (mm)	10 (4.8 - 15.2)	11.3 (9.1 - 13.5)	8.5 (6.4 - 10.5)	8.6 (6.9 - 10.4)	Ns
Pelvis area (cm2)	0.9 (0.5- 1.7)	2.9(0.6 – 3.6)	5.7 (2.4 - 8.9)	10.5 (2.1-18.7)	0.001
RSF(%)**	48.7 (44.2 – 53.2)	50 (46.4 - 53.5)	43.5 (29.2 - 57.8)	49.9 (45.9 - 53.8)	Ns
Renal demage	-	-	11(19.6)	-	

Ns=nonsignificant (p>0.05); RSF=Renal split function; †Data are expressed as mean (95% CI) or number(%); ‡Mild HN=grade 1-2 hydronephrosis; Severe HN= grade 3-4 hydronephrosis; HN in need for surgery grade 34*

We studied the agreement between US and scintigraphy, quantified using ICC, with a value of 0.87 (0.79 – 0.92), p<0.0001. The distributions of renal pelvic AP diameter of patients included in various classes of scintigraphy diagnosis were visually inspected through box plots. There was a significant difference (p=0.001) in mean (95% CI) APD at postnatal US scan between non-obstructive hydronephrosis [8.7 (5.22 – 12.27) mm], vesico-ureteral reflux [8.83 (4.18 – 14.48)mm], primary megaureter [10.58 (5.78 – 15.39)mm] and uretero-pelvic junction obstruction [19 (14.73 – 23.26)mm] (fig. 1).

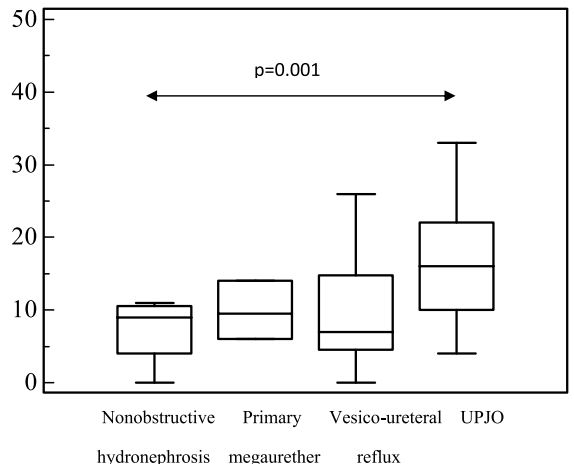


Fig 1. Mean and 95% CI of pelvis APD at postnatal US scan for nonobstructive hydronephrosis, primary megaureter, vesico-ureteral reflux and uretero-pelvic junction obstruction

Ultrasound parameters are the most important predictors of hydronephrosis, therefore we analyzed how these parameters influence the scintigraphy hydronephrosis grades. Ultrasound AP diameter values were significantly correlated with two other ultrasound and one scintigraphy measurements; we found correlations with US parenchyma values (r=0.59, p=0.001), pelvis area (0.76, p=0.001) and with scintigraphy long axis measurements (r=0.89, p=0.001). In multiple regression analysis, adjusted for age and sex, only the APD independently influenced the presence of severe hydronephrosis, in need of surgery (p<0.001). The pelvis APD explained 62.4% of the variance of hydronephrosis (R2=0.624, p<0.001). The ROC curves for postnatal ultrasound APD was plotted, and the area under the curve (AUC) was calculated. After the analysis of the basic statistical parameters and the ROC curves, the ideal APD cut-off for detection of significant hydronephrosis was 11 mm or more, and for detection of severe, high grade hydronephrosis, in need for surgery, was 19 mm or more.

In figures 3 and 4 we presents the ultrasonographic and scintigraphic aspect in a 4 months boy with UPJO.

The reflux nephropathy in a 8 months girl with VUR is illustrated in fig 5 and 6.

Transperineal ultrasonography in a 6 days old boy with PUV is presented in fig 7.

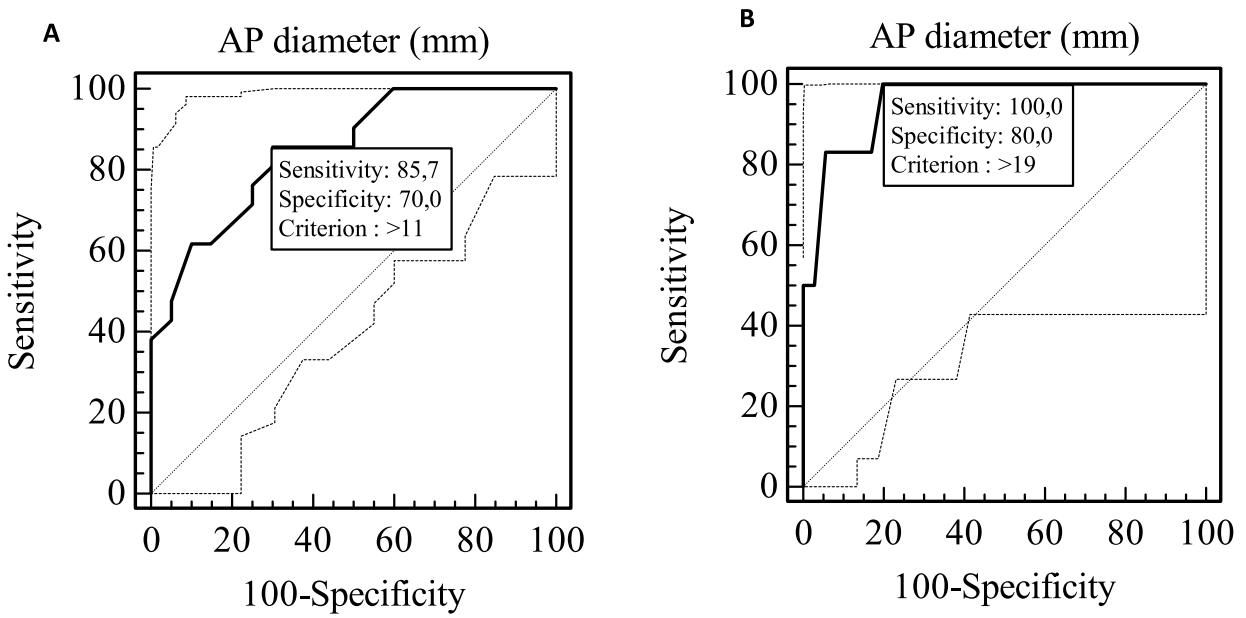


Fig 2. ROC curves for pelvis APD for different hydronephrosis grades: A. Mild (grade 1, 2) vs severe (grade 3, 4); B. Conservative treatment (including grade 1, 2, 3) vs Hydronephrosis in need for surgery (including grade 3, 4).

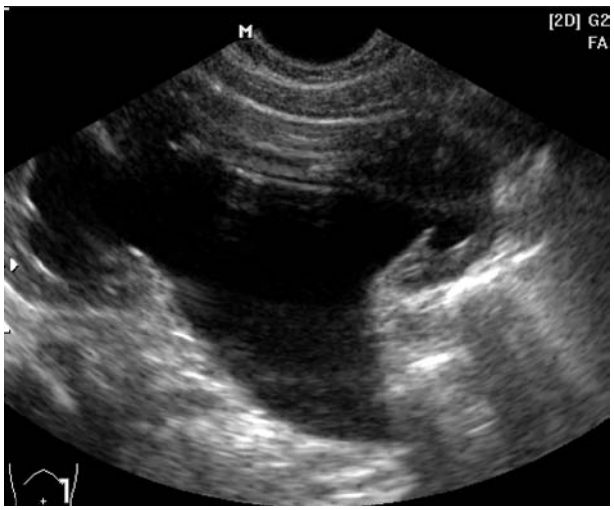


Fig 3. Left kidney ultrasound (coronal longitudinal scan) reveals an important hydronephrosis with very thin renal parenchima (ureteropelvic jonction obstruction).

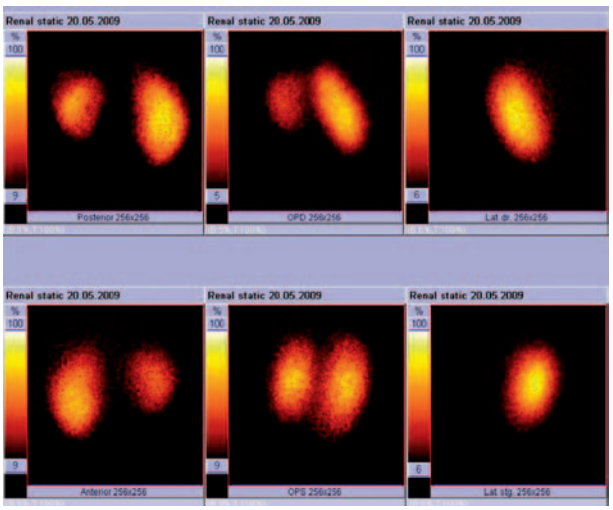


Fig 6. 99mTc – DMSA renal scintigraphy: left reflux nephropathy with a renal differential function 31% left kidney and 69% right kidney.

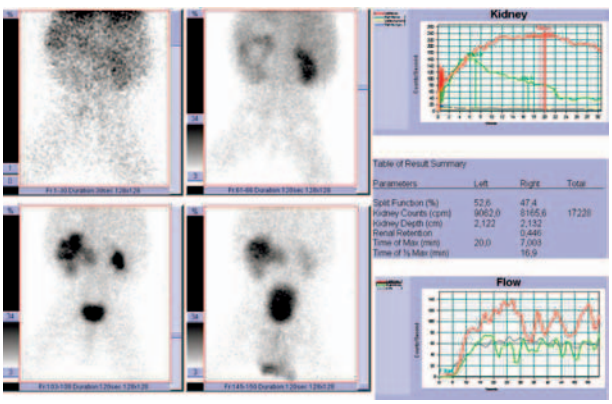


Fig 4. Renal diuretic scintigraphy in the patient from figure 3 shows an important pelvis and calyces dilation and a delay in the evacuation after Furosemide (diagnosis is ureteropelvic junction obstruction, IIIrd degree).

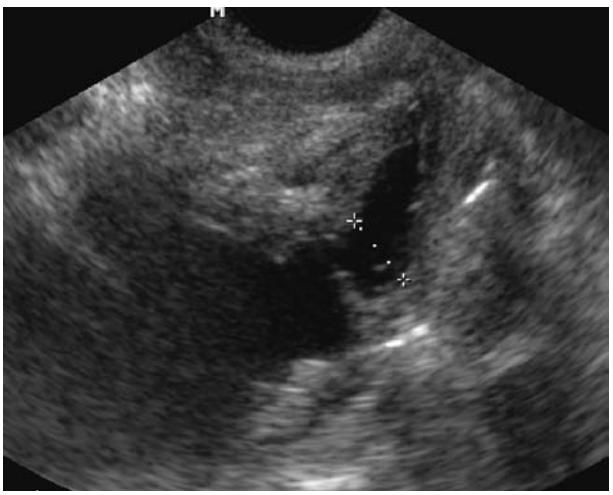


Fig 7. Transperineal scan in an posterior urethral valve shows a large proximal urethra and a thick urinary bladder wall.

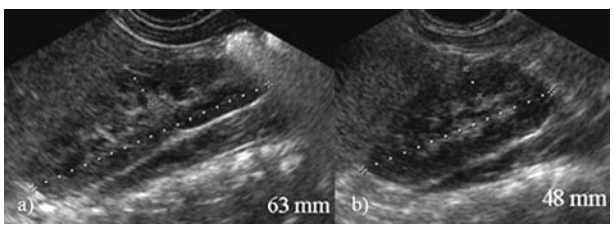


Fig 5. a) Right kidney ultrasonography - longitudinal view: normal kidney with a 63 mm longitudinal diameter; b) Left kidney ultrasonography – longitudinal view shows a small kidney with reflux nephropaty (48 mm longitudinal diameter).

Discussions

Ultrasound is a promising clinical method for the rapid and non-invasive assessment of congenital renal abnormalities. The ideal diagnosis algorithm is currently subjected to extensive validation in cross-sectional and longitudinal studies, both for diagnosis and monitoring the response to conservative or surgical treatments [2,12]. Why should we test again the ultrasound accuracy? A major scope in this process of validation concerns the identification of potential factors leading to an over- and under-estimation of renal damage assessed by this technique. In this context, important ultrasound measure-

ments could represent important confounding factors in patients with reno-urinary malformations. In our studied group the incidence of renal and urinary tract anomalies was 0.51% and 2.75% respectively. These findings are consistent with those already published [13.14], even if it is hard to compare their incidences. Studies concerned with screening for renal malformations use various methods and groups of patients [15]. Most of them use ultrasound as a screening method. Prenatal detection of severe abnormalities was extremely low in our study with positive prenatal screening results in 1.21%. The value of antenatal ultrasound as a screening modality is controversial [16,17]. The presence of isolated mild renal pelvis dilatation is a common observation during antenatal US examination and its postnatal management is disputed [18]. In most studies, the accuracy of pelvis APD is assessed [14,19,20]. They report values for estimated areas under the curve (AUC) with high sensitivity and specificity for pelvis APD as an excellent test for discriminating between clinically significant and no significant uropathy. However none of these studies have been designed to evaluate the accuracy of more postnatal US parameters, other than APD.

To overcome these shortcomings, we analysed a series of ultrasonography and scintigraphy parameters at hand. The agreement between ultrasound and scintigraphy was quantified using the two-way mixed interclass correlation coefficient (ICC). The ICC quantifies the agreement between two measurements as poor (ICC=0.00-0.20), fair to good (ICC=0.40-0.75) or excellent (ICC>0.75) [21]. The agreement in the present study was quantified as excellent (ICC=0.87). First, in patients with urinary tract malformations, pelvis AP diameter was found to be highly correlated with the US parenchyma values, pelvis area and with scintigraphy long axis measurements. In multiple regression analysis, the AP diameter independently influenced the presence of high grade hydronephrosis, regardless of age and sex. Parenchyma thickening does not seem to influence the grade of HN in patients. These findings sustain the idea that parenchyma narrowing is better assessed using other imaging techniques, like DMSA scintigraphy or IRM. Kavanagh et al claimed renal MRI as a rapid, accurate and minimally invasive technique of renal defects that does not employ ionizing radiation, compared with scintigraphy as gold standard. Further studies are needed to elucidate this matter [22,23].

The pelvis APD explained by itself 62.4% of the variance of hydronephrosis. The size and the direction of the relationship suggest that higher values of APD are obtained for patients with advanced renal disease. Between the investigated parameters, this measurement is the single most important predictor, as suggested by the squared partial correlation. This result was an expected one, but other parameters cannot be neglected, and might explain the hydronephrosis variability. It should be mentioned that in our group we did not demonstrate the diagnostic accuracy of APD that might influence the variability within the same renal anomaly. For example, many studies have demonstrated that, whatever the grade, US is a poor predictor of vesico-ureteral reflux [24]. In our series, as seen in table II, the APD of renal units from a single postnatal US scan was unable to predict the presence or severity of reflux. The pelvis APD of renal units with reflux presented the greatest dispersion, with values raging between 5.7-15.3.

When we focused on the diagnosis of high grade hydronephrosis, the APD performances were very good. The area under ROC curve for the diagnosis of mild vs. severe HN and for the diagnosis of patients in need for surgery, were 0.86 and 0.95 respectively. The diagnostic performance of ultrasound was similar to those previously published by other authors [25,26,27].

Our findings support the idea that pelvis APD has high influence on the hydronephrosis grade, but, as stated before, the role of other parameters cannot be neglected. Taking into account the cut-off values obtained, we can suggest that finding a dilated renal pelvis with an AP diameter greater than 19 mm is a good indicator for further investigations to evaluate the need for surgery. In a previous published study on patients with IInd-IVth grade unilateral congenital hydronephrosis, Fufezan et al revealed that early surgical treatment allowed for better

Table III. Pelvis APD cut-off values for different hydronephrosis grades assesed by scintigraphy.

	Mild vs severe HN	**Conservative vs need for surgery**
APD cutoff value (mm)	11	19
Se(%) (95% CI)	85.7 (63.7-97)	100 (54.1 -100)
Sp (95% CI)	70 (45.7 – 88.1)	80 (63.1 – 91.6)
+LR	2.86	5
-LR	0.20	0
PPV	75	46.2
NPV	82.4	100
AUROC (95% CI)	0.86	0.95
SE	0.05	0.06
Accuracy	0.78	0.89
Significance level p	0.00001	0.0001

Se sensitivity, Sp specificity, PPV positive predictive value, NPV negative predictive value CI confidence interval, +LR Positive likelihood ratio, -LR Negative likelihood ratio, SE standard error, AUROC area under ROC curve

improvement of the renal parenchyma, in contrast with cases when it was performed after the age of 3. The study also showed that monitoring of mild hydronephrosis did not lead to the alteration of the renal parenchyma. On the other hand, in cases where the surgical intervention was delayed (parent's refusal), a significant impairment of the renal parenchyma was observed [28]. Considering these observations, a balance should be found between invasive and conservative treatment. In relation to other diagnostic indices or predictive models based on laboratory tests, the ultrasound evaluation based on pelvis APD has some leading advantages: it is easy to use, non-invasive and painless, does not imply anaesthesia and thus it is easily accepted by the paediatric patients. The results are available immediately but dependent by the operator. Regardless of this limitation of US, high grade hydronephrosis could be assessed properly through this method. Our findings can represent valuable evidence, since the cohort of patients is well documented.

Conclusions

Our findings suggest that ultrasound is a useful non-invasive method for assessment of renal anomalies in paediatric patients. We have demonstrated the relationship between AP diameter and severity of hydronephrosis. This diameter is the main predictor of hydronephrosis, but pelvis area, renal length and parenchyma thickening also influence it.

The antero-posterior diameter of the pelvis explained 62.4% of the variance of hydronephrosis. Further studies are required in order to identify all the parameters that might influence the presence of renal abnormalities, both radiological and biochemical, for a better, complete and non-invasive evaluation. The use of 3D ultrasound might represent a big step forward towards the goal of a "virtual renal biopsy".

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