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Prenatal diagnosis of LUTO: improving diagnostic accuracy

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KEYWORDS: lower urinary tract obstruction; LUTO; megacystis; prenatal diagnosis

ABSTRACT

Objective To propose a clinical score for the optimal antenatal diagnosis of fetal lower urinary tract obstruction (LUTO) in the second and third trimesters of pregnancy, as an alternative to the commonly used ultrasound triad of megacystis, keyhole sign and hydronephrosis.

Methods This was a national retrospective study carried out at the eight tertiary fetal medicine units (FMUs) in The Netherlands. Only cases referred for megacystis from the second trimester onwards and with a clear postnatal diagnosis were included in the study. At referral, data were collected on amniotic fluid volume, renal cortical appearance, bladder volume, hydronephrosis, fetal ascites, ureteral size, keyhole sign, fetal sex and gestational age. Multivariate analysis was performed, starting by including all antenatal variables, and then excluding the weakest predictors using the backward stepwise strategy.

Results Over a 7-year period, 312 fetuses with a diagnosis of megacystis were referred to the eight Dutch tertiary FMUs. A final diagnosis was achieved in 143 cases, including 124 of LUTO and 19 reclassified after birth as non-obstructive megacystis. The optimal bladder volume cut-off for prediction of LUTO was 35 cm³ (area under the curve (AUC) = 0.7, P = 0.03). The clinical score formulated on the basis of the multivariate analysis included fetal sex, degree of bladder distension, ureteral size, oligo- or anhydramnios and gestational age at referral. The combination of these five variables demonstrated good accuracy in discriminating LUTO from non-obstructive megacystis (AUC = 0.84, P < 0.001), compared with the poor performance of the ultrasound triad (AUC = 0.63, P = 0.07).

Conclusions We propose a clinical score that combines five antenatal variables for the prospective diagnosis of congenital LUTO. This score showed good discriminative capacity in predicting LUTO, and better diagnostic accuracy compared with that of the classic ultrasound triad. Future studies to validate these results should be carried out in order to refine antenatal management of LUTO and prevent inappropriate fetal interventions. © 2017 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

The term lower urinary tract obstruction (LUTO) refers to a heterogeneous group of anatomical anomalies causing an obstruction in the urethra. During fetal life, LUTO entails a sequence of events that are detectable on antenatal ultrasound examination. This typically starts with evidence of a distended bladder (megacystis) accompanied by hydronephrosis, progressing to renal dysplasia with abnormal renal parenchymal appearance on ultrasound examination and eventually resulting in...
severe oligohydramnios. The condition is associated with a high rate of mortality and postnatal morbidity due to lung hypoplasia and impaired renal function. When LUTO is suspected in the first trimester and megacystis >12 mm is seen, the prognosis is extremely poor and parents often opt for termination of pregnancy. For cases identified later in pregnancy, no definitive criteria for diagnosing LUTO and predicting the precise prognosis have yet been proposed. Beyond the first trimester, the diagnosis of LUTO is typically based on the evidence of three ultrasound findings: megacystis, dilated posterior urethra (known as the keyhole sign), and either unilateral or bilateral hydronephrosis.

Over the past 20 years, fetal therapy has been attempted based on the assumption that, by relieving the intracavitary pressure caused by the obstruction, mortality and renal damage could possibly be prevented. The LUTO trial investigated this assumption, demonstrating a significant improvement in survival of fetuses treated with vesicoamniotic shunt, but reporting a high rate of morbidity among survivors, irrespective of the antenatal management. To date, whether and when in-utero treatment should be offered remains a matter of debate, and the eventual selection of candidates is still suboptimal, owing to the high number of false-positive LUTO cases.

In fact, a previous study reported that one-third of all LUTO cases suspected prenatally are reclassified postnatally, primarily to vesicoureteral reflux. For this reason, an improvement in the diagnostic accuracy of ultrasound for LUTO is called for.

The aim of this study was to identify the optimal combination of ultrasound parameters for the antenatal diagnosis of LUTO from the second trimester, as an alternative to the commonly used LUTO triad (megacystis, keyhole sign and hydronephrosis).

METHODS

This was a retrospective national study carried out at all eight fetal medicine units (FMUs) of university hospitals in The Netherlands. Cases were collected according to the start of registration in databases; this was from 2000 to 2015 in three centers (Erasmus Medical Center, Rotterdam; Academic Medical Center, Amsterdam; University Medical Center, Maastricht), from 2004 to 2015 in two centers (University Medical Center Groningen and Radboud University Medical Center, Nijmegen), and between 2007 and 2014 in the remaining centers (Leiden University Medical Center, Leiden; Utrecht University Medical Center, Utrecht; VU University Medical Center, Amsterdam). These FMUs act as expert referral centers for all anomalies suspected at peripheral hospitals and external ultrasound clinics in The Netherlands. We included only cases referred for fetal megacystis diagnosed from 18 weeks’ gestation onwards, and therefore either directly after the routine second-trimester examination or after an ultrasound examination performed later in pregnancy for growth or other obstetric indications. Fetal megacystis was defined as an enlarged bladder failing to empty during an extended ultrasound examination lasting at least 40 min.

The following antenatal data were collected at referral: gestational age, fetal sex, evidence of keyhole sign or fetal ascites (caused by leakage or rupture of the distended bladder), hydronephrosis, amniotic fluid volume, renal cortical appearance, right and left ureteral diameters, and anteroposterior, transverse and longitudinal bladder diameters. Bladder volume was calculated using the formula: \( \text{bladder volume} = \pi \times \frac{1}{6} \times \sum (\text{transverse diameter} \times \text{longitudinal diameter}) \). The sum of right and left ureteral diameters was calculated for each case, and for ureters non-visualized at the ultrasound examination the sum was considered to be 0 mm. Amniotic fluid volume was considered reduced in cases of a single deepest pocket of <2 cm. Ultrasound reports were reviewed in order to retrieve data on amniotic fluid volume, renal pelvis dilatation and renal parenchymal echogenicity. Only the first detailed ultrasound report at referral was used for analysis.

Outcome data included all available postnatal data on surgeries and medical examinations for liveborn infants, and postmortem examinations for perinatal deaths, when available. The term LUTO referred to a group of anatomical anomalies causing urethral obstruction. This group thus included cases with posterior urethral valves (PUV), urethral stenosis, urethral atresia and also cases with LUTO reported as the final diagnosis but without further details concerning the type of obstruction (non-specified LUTO).

Antenatal baseline characteristics were compared using the chi-square test or Fisher’s exact test for categorical variables and the Student’s t-test for continuous variables. Univariate analysis was performed to examine the association between candidate predictors and final diagnosis. A logistic model was developed, first considering eight variables, and then using the backward stepwise strategy to exclude progressively the weakest predictors. Model performances were assessed using the Hosmer–Lemeshow test for goodness of fit, and the discriminative performance of the models was evaluated by the area under the receiver–operating characteristics (ROC) curve (AUC) using the predicted and the actual outcomes. The model was validated internally with bootstrapping using R-project software 3.4.2 (https://www.r-project.org/package.rms).

A clinical score was developed based on the results of the logistic model. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated. Data analyses were performed using the statistical software package SPSS Statistics 23 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, in total, 312 pregnancies were referred because of suspected fetal megacystis from the 18th week onwards. The outcomes of the 312
pregnancies were 71 terminations of pregnancies, 10 cases of intrauterine fetal death, 38 neonatal deaths and 193 liveborn infants. Ninety-eight cases (31%) were excluded from the study because of missing or incomplete data preventing a final diagnosis (in 55 cases autopsy was declined and 43 cases were lost to follow-up) and 68 cases (22%) were excluded because of incomplete antenatal data or measurements. Moreover, three megacystis cases not suspected of being LUTO were excluded from further analysis, all of which presented polyhydramnios and macrosomia, and an overgrowth syndrome was confirmed after birth (Figure 1).

Based on postnatal investigations or postmortem examinations, a final diagnosis was achieved in 143 cases, including 124 (87%) true LUTO cases (74 PUV, four urethral atresia, six urethral stenosis and 40 non-specified LUTO) and 19 (13%) cases reclassified postnatally as non-obstructive megacystis (12 infants with vesicoureteral reflux, four cases of primary mega-ureters, one fetus with megacystis-microcolon-intestinal hypoperistalsis syndrome, and two cases without any evidence of urological anomaly and with normal voiding at birth).

Descriptive statistics, sensitivity, specificity and results of the univariate analysis according to final diagnosis are presented in Tables 1 and 2. Longitudinal bladder diameter showed poorer accuracy on univariate analysis compared with bladder volume, and was therefore excluded from further analysis. A ROC curve of bladder volume was used to identify the optimal cut-off for prediction of LUTO (AUC = 0.66; 95% CI, 0.6 – 0.8; P = 0.03; optimal cut off, 35 cm$^3$). In addition, 13 cases showed urinary ascites at referral with a collapsed urinary bladder, suggesting that the severely enlarged bladder had ruptured, thus making bladder volume measurement no longer reliable. Therefore, severe megacystis was defined by a bladder volume > 35 cm$^3$ or ascites at referral.

Multivariate logistic regression analysis was performed, starting with the inclusion of the following antenatal variables considered as theoretically relevant in the literature for the prospective diagnosis of LUTO: renal cortical appearance (normal or abnormal); amniotic fluid volume (normal or reduced); gestational age at referral (< or ≥ 28 weeks’ gestation); hydronephrosis, degree of bladder distension (mild or severe); fetal sex (female or male); evidence of keyhole sign (yes or no); and ureteral diameter as a continuous variable. The stepwise backward method resulted in the progressive elimination of variables with poorer performance. These variables were fetal hydronephrosis, renal cortical appearance and keyhole sign.

The final model included five predictive variables: severe megacystis (odds ratio (OR), 4.21 (95% CI, 0.98 – 18.21); P = 0.054; after bootstrapping; P = 0.052); ureteral size (OR, 1.25 (95% CI, 1.02 – 1.54); P = 0.035; after bootstrapping: P = 0.029); oligohydramnios (OR, 3.7 (95% CI, 0.71 – 19.25); P = 0.12; after bootstrapping: P = 0.04); and referral before the 28th week (OR, 3.72 (95% CI, 1.18 – 11.72); P = 0.025; after bootstrapping: P = 0.019). The Hosmer–Lemeshow test for goodness of fit showed a good fit of this model with $P = 0.94$, considering that $P$-values closer to 1 indicate a better fit. The

Table 1 Antenatal ultrasound characteristics in 143 cases referred from second trimester for fetal megacystis, according to final diagnosis

| Characteristic | Non-obstructive megacystis (n = 19) | LUTO (n = 124) | P  
|----------------|-------------------------------------|----------------|------
| Male fetal sex | 14 (74) | 115 (93) | 0.01  
| Keyhole sign   | 5 (26)  | 59 (48)  | 0.08  
| Echogenic kidneys | 4 (21)  | 67 (54)  | < 0.01  
| Oligo- or anhydramnios | 2 (11)  | 55 (44)  | < 0.01  
| Hydronephrosis | 15 (79) | 108 (87) | 0.29  
| Referral < 28 weeks | 8 (42) | 82 (66) | 0.04  
| Gestational age at referral (weeks) | 25 (19–36) | 23 (18–36) |  
| Bladder volume (cm$^3$) | 18 (0.7–58) | 31 (0.3–390) | < 0.01  
| Bladder longitudinal diameter (mm) | 36 ± 13 | 45 ± 18 | 0.03  
| Ureteral size* (mm) | 1.8 ± 3.5 | 5.3 ± 7.2 | < 0.01  

Data are given as n (%), median (range) or mean ± SD. * Sum of right and left ureteral diameters. LUTO, lower urinary tract obstruction.

Table 2 Univariate analysis, sensitivity and specificity of variables for antenatal diagnosis of lower urinary tract obstruction in 143 fetuses referred from second trimester for megacystis

| Variable | OR (95% CI) | Sensitivity (%) | Specificity (%) |
|----------|-------------|----------------|----------------|
| Male fetal sex | 4.56 (1.3–15.6) | 93 | 26  
| Keyhole sign | 2.54 (0.8–7.5) | 48 | 74  
| Echogenic kidneys | 4.41 (1.4–14.0) | 54 | 79  
| Oligo- or anhydramnios | 6.78 (1.5–30.6) | 44 | 90  
| Referral < 28 weeks | 2.69 (1.0–7.2) | 66 | 58  
| Hydronephrosis | 1.92 (0.6–6.6) | 88 | 21  
| Severe megacystis* | 5.16 (1.4–18.6) | 49 | 84  

*Bladder volume > 35 cm$^3$ or ascites. OR, odds ratio.
optimism-corrected model performance after bootstrapping was 82%, 2% smaller than for the original dataset.

A clinical score was formulated based on the results of the logistic regression model (Table 3). Figure 2 shows the accuracy of this proposed clinical score in discriminating LUTO from non-obstructive megacystis, compared with that of a theoretical model based only on the commonly used LUTO triad (AUC, 0.84 (95% CI, 0.75–0.93; P < 0.001) vs 0.63 (95% CI, 0.49–0.77; P = 0.07)). ROC curve analysis identified 9.5 as the optimal cut-off point for the clinical LUTO score in predicting the risk of LUTO. At this cut-off, the risk of LUTO was 96%, sensitivity was 78% (95% CI, 70–85%), specificity was 79% (95% CI, 54–94%), PPV was 96% (95% CI, 91–98%) and NPV was 36% (95% CI, 27–46%).

### DISCUSSION

In this study, we proposed a clinical score for calculating the risk of congenital LUTO during pregnancy, based on five antenatal variables all evaluated at the detailed ultrasound examination at referral: bladder distension (severe or moderate); bilateral ureteral dilatation (as a continuous variable); amniotic fluid volume (normal, or oligo- or anhydramnios); fetal sex; and gestational age at referral (< or ≥ 28th week). This score demonstrated good discriminative value in distinguishing true LUTO from non-obstructive megacystis, which would not be amenable to antenatal treatment, and a better performance than that of the classic antenatal triad. The use of this new combination of ultrasound parameters enables optimal identification of LUTO cases at the time of referral, allowing for appropriate counseling and management options.

The role of fetal therapy for LUTO is still debated in the literature and the opportunity to gain high-quality evidence has been missed due to the premature conclusion of the PLUTO trial. A retrospective multicenter study was published recently with the aim of exploring the effectiveness of fetal therapy in cases with severe LUTO, defined as megacystis, increased bladder-wall thickness, bilateral severe hydronephrosis and oligohydramnios. Despite the strict criteria, 23% of treated fetuses were wrongly suspected of having LUTO. We think that both disease severity and selection of candidates for in-utero treatment are influential determinants of the effectiveness of fetal therapy, and that an improvement in the diagnostic accuracy of antenatal ultrasound is thus needed.

In this study, fetal hydronephrosis was observed in 88% of LUTO cases and in 79% of non-obstructive megacystis cases. A recent review reported hydronephrosis in only 40–50% of LUTO cases and questioned the strength of this association. The keyhole sign demonstrated high specificity (74%) but poor sensitivity (48%) for LUTO (Table 2). Other studies have reported previously poor accuracy of this ultrasound sign for the prospective diagnosis of LUTO, in particular PUV. It has been hypothesized that a possible explanation for its low reliability is that miscellaneous types of bladder dysfunction, such as detrusor instability and bladder-sphincter dyssynergia, can cause dilatation of the bladder neck. The latter has in fact been diagnosed on voiding cystourethrogram in 30% of male infants with vesicoureteral reflux. Dilatation of the bladder neck on prenatal ultrasound examination could mimic a dilated posterior urethra, with an ultrasound appearance similar to a keyhole, without being a true dilatation of the posterior urethra. Therefore, although the keyhole sign and hydronephrosis have thus far been considered as key findings of LUTO, and of PUV in particular, they have poor predictive performance for the exact postnatal diagnosis.

Amniotic fluid volume was included in the final model, although it demonstrated poor sensitivity on univariate analysis. In fact, in our cohort, 69/124 (56%) of LUTO cases showed normal amniotic fluid at referral. This is consistent with previous studies that reported a rate of 39%, although they did not set a specific gestational age for evaluating this parameter. Oligohydramnios is
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To conclude, in order to improve the diagnostic accuracy of LUTO in the second and third trimesters, the criteria that need to be evaluated are fetal bladder enlargement, ureteral dilatation, gestational age at referral, fetal sex and evidence of oligo- or anhydramnios. Future studies validating externally these results are needed in order to refine the antenatal identification of LUTO, prevent unnecessary fetal interventions and optimize prenatal management.

REFERENCES

1. Lissaunder D, Morris RK, Kilby MD. Fetal lower urinary tract obstruction. Semin Fetal Neonatal Med 2007; 12: 464–470.
2. Anumba DO, Scott JE, Plant ND, Robson SC. Diagnosis and outcome of fetal lower urinary tract obstruction in the northern region of England. Prenat Diagn 2005; 25: 1121–1123.
3. Morris RK, Kilby MD. Congenital urinary tract obstruction. Best Pract Res Clin Obstet Gynaecol 2008; 22: 97–122.
4. Fontanella F, Don L, Adami van, Helema PN, Cohen-Overbeek TE, Pijlert E, Bekker M, Wilkesen C, Bas CJ, Bilardo CM. Fetal megacystis: prediction of outcome and spontaneous resolution. Ultrasound Obstet Gynecol 2017; 50: 458–463.
5. Seibert NJ, Van Kaisenberg C, Rubio C, Sniiders RJM, Nikolaides KH. Fetal megacystis at 10–14 weeks of gestation. Ultrasound Obstet Gynecol 1996; 8: 387–390.
6. Ruano R, Sananes N, Sango-Hadjpyekar H, Hernandez-Ruano S, Moog R, Becmeur F, Zaloysy A, Guion AM, Morin B, Fave R. Fetal intervention for severe lower urinary tract obstruction: A multicenter case–control study comparing fetal cystoscopy with vesicouretic reflux shunting. Ultrasound Obstet Gynecol 2015; 45: 452–458.
7. Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Hemming K, Burke D, Daniels JP, Khan KS, Deeks J, Kilby MD; Pervicoureteric vesicouretic shunting in Lower Urinary Tract Obstruction (PLUTO): Collaborative Group. Percutaneous vesicoureteral shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): A randomised trial. Lancet 2013; 382: 1496–1506.
8. 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: 382–390.
9. Malin G, Tonks AM, Morris RK, Gardosi J, Kilby MD. Congenital lower urinary tract obstruction: A population-based epidemiological study. BJOG 2012; 119: 1455–1464.
10. Campbell S, Wladimiroff JW, Dewhurst CJ. The antenatal measurement of fetal urine production. J Obstet Gynaecol Br Communs 1975; 80: 480–488.
11. Haeri S. Fetal Lower Urinary Tract Obstruction (LUTO): A practical review for providers. Mater Heal Neonatal Perinatal 2015; I: 26.
12. Chriri Y, Bourron M, Korb D, Grapin-Dagorn C, Jostau-Zovorinski F, Vuillard E, Paye-Jassuer A, Pecconel M, Beladi N, Delozaude AL, Schmitz T, El Ghoneimi A, Sibony O, Oury JF. Posterior urethral valves and vesicouretic reflex: can prenatal ultrasonography distinguish between these two conditions in male fetuses? Prenat Diagn 2016; 36: 831–837.
13. Bernardes LS, Aknes G, Saada J, Masse V, Elie C, Dumez Y, Lortat-Jacob SL, Benachi A. Keyhole sign: How specific is it for the diagnosis of posterior urethral valves? Ultrasound Obstet Gynecol 2009; 34: 419–423.
14. Cohen HL, Zinn HL, Patel A, Zinn DL, Haller JO. Prenatal sonographic diagnosis of posterior urethral valves: identification of valves and thickening of the posterior urethral wall. J Clin Ultrasound 1995; 23: 366–370.
15. Boopathi Vijayaraghavan S. Sonography of fetal megalocystis. Ultrasound Obstet Gynecol 2004; 24: 659–663.
16. Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-urethric reflex in male and female infants with pre-natal hydronephrosis. Br J Urol 1997; 80: 319–327.
17. Touboul C, Boivain M, Picone O, Levallant J-M, Frydman R, Senat M-V. Normal fetal urine production rate estimated with 3-dimensional ultrasonography using the rotational technique (virtual organ computer-aided analysis). Am J Obstet Gynecol 2008; 199: 57.e1–57.e5.
18. Muller F, Deure S, Vaast P, Dumez Y, Nisand I, Ville Y, Boullet P, Guibaudencche J, Althusser M, Bin G, Gautier E, Lespain C, Perrotin F, Poulan P, Sarramon MF; Study Group of the French Fetal Medicine Society. Prenatal diagnosis of megalocystis-microcolon-intestinal hypoperistalsis syndrome: contribution of amniotic fluid digestive enzyme assay and fetal urinalysis. Prenat Diagn 2005; 25: 203–209.
19. Bornes M, Sparaggi E, Schmitz T, Deure S, Czarkiewicz I, Delozaude AL, El-Ghoneimi A, Oury JR, Muller F. Outcome and etiologies of fetal megacystis according to the gestational age at diagnosis. Prenat Diagn 2013; 33: 1162–1166.
20. Montemarano H, Bulas DI, Rushton HG, Selby D. Bladder distention and pyelectasis in the male fetus; causes, comparisons, and contrasts. J Ultrasound Med 1999; 17: 743–749.
21. Muller Brochot A-C, Thomann D, Kluwe W, Di Naro E, Kuhn A, Raio L. Fetal megacystis: experience of a single tertiary center in Switzerland over 20 years. Fetal Diag Ther 2014; 36: 215–222.
22. Robyr R, Benachi A, Daikha-Dahmane F, Martinovich J, Dumez Y, Ville Y. Correlation between ultrasound and anatomical findings in fetuses with lower urinary tract obstruction in the first half of pregnancy. Ultrasound Obstet Gynecol 2005; 25: 478–482.

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