



Prenatal diagnosis of LUTO: improving diagnostic accuracy

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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 cm^3 (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 urethra¹. 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

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severe oligohydramnios². The condition is associated with a high rate of mortality and postnatal morbidity due to lung hypoplasia and impaired renal function³. 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^{4,5}. For cases identified later in pregnancy, no definitive criteria for diagnosing LUTO and predicting the precise prognosis have yet been proposed⁶. 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 PLUTO 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 management⁷. 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 cases⁸. In fact, a previous study reported that one-third of all LUTO cases suspected prenatally are reclassified postnatally, primarily to vesicoureteral reflux⁹. 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 formula¹⁰: longitudinal diameter × transverse diameter × anteroposterior diameter × $\pi/6$. 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 obstruction¹. 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 $> 35 \text{ cm}^3$ 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: $P = 0.10$); male sex (OR, 4.09 (95% CI, 0.88–18.88); $P = 0.071$; 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 \pm 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 $> 35 \text{ cm}^3$ or ascites. OR, odds ratio.

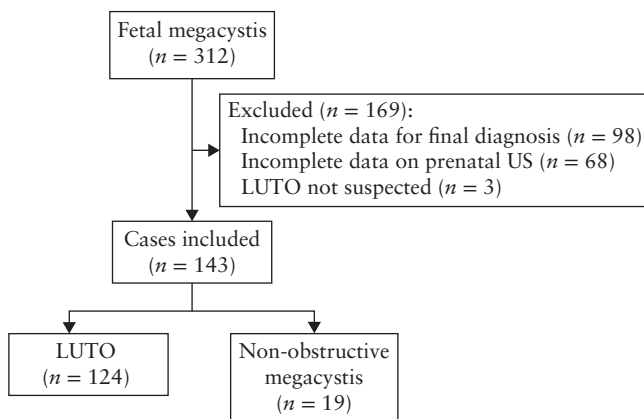


Figure 1 Flowchart of study population of patients referred for fetal megacystis. LUTO, lower urinary tract obstruction; US, ultrasound.

Table 3 Proposed clinical score for antenatal diagnosis of lower urinary tract obstruction (LUTO)

Variable	Points
Severe megacystis*	4
Bilateral ureteral diameters	1.3/mm†
Oligo- or anhydramnios	4
Male fetal sex	4
Referral < 28 weeks	4

Score of ≥ 9.5 indicates LUTO. *Bladder volume $> 35 \text{ cm}^3$ or ascites. †Value for each mm of ureteral size.

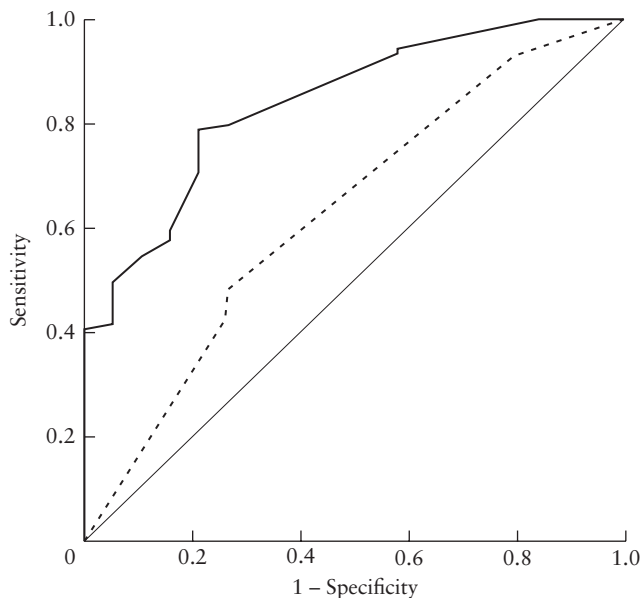


Figure 2 Receiver–operating characteristics curves for antenatal diagnosis of lower urinary tract obstruction (LUTO) in 143 fetuses referred from second trimester for megacystis, based on LUTO clinical score (—; area under the curve (AUC), 0.84; 95% CI, 0.75–0.93; $P < 0.001$) and based on classic LUTO triad (- - - -; AUC, 0.63; 95% CI, 0.49–0.77; $P = 0.07$).

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 $\geq 28^{\text{th}}$ 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 LUTO⁶. 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 association¹¹. The keyhole sign demonstrated high specificity (74%) but poor sensitivity (48%) for LUTO (Table 2). Other studies^{12–14} 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 reflux¹⁵. 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^{13,16}. 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%¹³, although they did not set a specific gestational age for evaluating this parameter. Oligohydramnios is

typically considered as a characteristic finding of LUTO, as cases with non-obstructive megacystis are unlikely to develop such an anomaly. For this reason, reduced amniotic fluid volume is often used as an eligibility criterion for *in-utero* treatment. However, some fetal medicine experts argue that oligohydramnios occurs when renal parenchyma has already been severely damaged and, for this reason, *in-utero* treatment should rather be offered to candidates with normal or only moderately reduced amniotic fluid volume. Our results confirm that the amniotic fluid volume, evaluated at the first detailed ultrasound examination, can be used in evaluating the risk of LUTO. However, its absence should not rule out antenatal suspicion of LUTO.

Another notable finding of this study was that the severity of bladder distension is an independent predictor of LUTO. Our results showed that the likelihood of LUTO was four-fold higher (OR, 4.21; $P = 0.05$) in cases of severe megacystis, defined by bladder volume $> 35 \text{ cm}^3$ or fetal ascites at referral. Megacystis has always been considered a key feature of LUTO, with a high predictive value¹³. However, an objective threshold to define megacystis during the second and third trimesters is still lacking. Previous studies^{10,17} have investigated fetal urine production according to gestational age in healthy fetuses without reporting fetal bladder dimensions. Miscellaneous criteria have been used in the literature for defining megacystis in the second and third trimesters, ranging from bladder length $> 99^{\text{th}}$ percentile for gestational age in the absence of a nomogram¹⁸, to the most commonly used definition of fetal bladder failing to empty during a period of 45 min^{19–22}. There has not yet been a prospective study published that has elucidated normal bladder dimensions during the second and third trimesters of pregnancy and defined a threshold for pathological enlargement. This is, therefore, urgently needed.

A strength of this study is that, at variance with previous studies, the antenatal variables were combined in a multivariate analysis and only values recorded at referral were considered. In spite of the fact that this approach reduced our cohort to 143 cases, this is thus far the largest study in the literature on the antenatal diagnosis of LUTO.

This study also has some limitations. First, not all the antenatal variables were measured directly by the sonographer and, in a proportion of cases, the first author (F.F.) measured them retrospectively from stored pictures. This also meant that serial bladder measurements were not available in most cases. Second, the retrospective design meant that, for renal parenchymal appearance, we had to rely upon the subjective judgment detailed in ultrasound reports, rather than on an objective measurement. This limitation may have affected the accuracy of this variable.

Statistical bootstrapping showed that overfitting of the model was small, suggesting that the model could hold for the overall population suspected to have LUTO. However, external validation is essential before endorsing this statement and supporting its clinical applicability.

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.

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