Antenatal diagnosis and management of fetal megacystis and lower urinary tract obstruction
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Antenatal Staging of congenital Lower Urinary Tract Obstruction (LUTO)

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Abstract

Aim: To propose a staging system for congenital Lower Urinary Tract Obstructions (LUTO) capable of predicting the severity of the condition and its prognosis.

Methods: This was a national retrospective study carried out at the eight Academic Hospitals in the Netherlands. We collected prenatal and postnatal data of fetuses at high-risk of isolated LUTO and managed conservatively. Postnatal renal function was assessed by the estimated glomerular filtration rate (eGFR), calculated with the Schwartz formula, considering the length of the infant and the creatinine nadir in the first year of age. Receiver operating characteristic (ROC) curve, univariate analysis and multivariate logistic regression analysis with stepwise backward elimination were performed in order to identify the best antenatal predictors of perinatal mortality and postnatal renal function.

Results: In total 261 fetuses suspected for LUTO and managed conservatively were included in the study. The pregnancy was terminated in 110 cases and perinatal death occurred in 35 cases. GA at the appearance of oligohydramnios showed an excellent accuracy in predicting the risk of perinatal mortality with an area under the curve of 0.95 (p < 0.001) and an optimal cut-off at 26 weeks’ gestation. Fetuses with still normal AF at 26 weeks’ 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. ROC analysis identified a BV of 5.4 cm³ at 20 weeks as the best threshold for predicting an adverse outcome. Therefore, LUTO cases with a BV ≥ 5.4 cm³ or abnormal AF before 20 weeks’ gestation were defined as severe and those with BV < 5.4 cm³ and still normal AF at the 20 weeks’ scan were defined as moderate. Risk of perinatal mortality significantly increased according to the stage of severity from mild to moderate and severe stage, from 8%, to 26% and to 55%, respectively. Similarly, risk of severely impaired renal function increased from 11%, to 31% and to 44%, respectively.

Conclusions: Gestational age at first appearance of oligo- or anhydramnios and bladder volume at diagnosis can accurately predict mortality and morbidity in fetuses with LUTO.
**Introduction**

The term lower urinary tract obstruction (LUTO) describes a heterogeneous group of conditions in which the normal urethral egress of urine from the fetal bladder is impaired (1). LUTO occurs in approximately 3 out of 10,000 pregnancies (2) and is associated with high mortality and morbidity due to pulmonary hypoplasia and progressive renal dysfunction, with the first being the main cause of perinatal death.

Natural history of LUTO is highly variable and depends on the severity of the disease, its duration and gestational age at onset of the obstruction (3). Fetuses with severe forms of LUTO present with massive bladder distention, hydronephrosis and renal dysplasia (4). From approximately 18 weeks’ gestation, when over 90% of the amniotic fluid (AF) is provided by fetal urine (5), severe LUTO also leads to oligohydramnios with secondary lung hypoplasia and soft tissue deformities, such as limb contractures, club feet, wide-set eyes, low-set ears and micrognathia (Potter sequence) (6). Conversely, fetuses with milder forms of LUTO can even preserve approximately normal AF amount throughout pregnancy and favorable renal function after birth (7). To date, natural history and prognosis of LUTO is unpredictable and there is no consensus over a staging system capable of predicting the severity of LUTO and the prognosis of these fetuses.

Moreover, an accurate prediction of the disease severity is probably the most powerful determinant of prognosis and is likely to strongly influence the effectiveness of fetal therapy in LUTO (8)(9). To date, the vesico-amniotic shunt (VAS) placement has demonstrated to improve perinatal survival (10), with an unclear role for preventing renal damage (11). To date, this intervention is often offered to severe megacystis cases with reduced amniotic fluid (7). However, oligohydramnios occurs often when fetal renal parenchyma has already been damaged, and this may heavily compromise the effectiveness of fetal-therapy on postnatal renal function.

Aim of this study was to propose a staging system capable of reliably predicting at the first ultrasound scan the severity of LUTO and its prognosis in order to appropriately counsel parents and triage cases eligible for a meaningful in-utero treatment.
Methods

This was a national retrospective study carried out at the eight tertiary care hospitals in the Netherlands from 2007 to 2014. Included were fetuses managed conservatively and at high-risk of isolated LUTO according to the criteria proposed in two previous studies from our cohort (12)(unpublished data):

- Fetuses referred before the 18th week of gestation (Early Megacystis) were included in case of: longitudinal bladder diameter greater than 12 mm, normal NT or normal karyotype and absence of umbilical cord cysts (unpublished data)
- Fetuses referred at or after the 18th week of gestation (Late Megacystis) were included in case of LUTO score greater than 9.5. The score was calculated by considering fetal sex, ureteral size, presence of oligohydramnios, bladder dimension or ascites (12).

Prenatal data were collected on amniotic fluid index (AFI), single deepest pocket (SDP), bladder volume, ureteral size, antero-posterior renal pelvis diameters, renal cortical appearance and gestational age (GA) at referral; lowest AFI throughout the pregnancy, and GA at first occurrence of oligohydramnios and abnormal renal cortical appearance. Oligohydramnios was defined by an amniotic fluid index (AFI) lower than 5 cm or maximum vertical pocket lower than 2 cm (13). The bladder volume was calculated using the formula: longitudinal diameter x transverse diameter x antero-posterior diameter x π/6 (14).

Postnatal data on outcome, GA and weight at birth were collected. All postnatal investigations and postmortem examinations were reviewed. Neonatal death was defined as deaths among live births during the first 28 completed days of life. Postnatal renal function was evaluated based on estimated glomerular filtration rate (eGFR), calculated with the Schwartz formula by considering the length of the infant and the creatinine nadir in the first year of diagnosis (15).

First, we tested by receiver operating characteristic (ROC) curve analysis the accuracy of GA at first appearance of oligohydramnios in predicting the risk of perinatal mortality. Second, we investigated by univariate analysis and multivariate logistic regression analysis with stepwise backward elimination the prognostic value of different antenatal US parameters at referral. Statistical analyses were carried out using SPSS 22 (IBM Corp., Armonk, NY, USA).
Results

In total 261 fetuses managed conservatively and at high-risk of isolated LUTO were included in the study. In 110 cases, owing to the uncertain prognosis, parents elected to terminate the pregnancy (mean GA: 23 weeks). Among the ongoing 151 pregnancies, perinatal mortality occurred in 35 cases (23%), including 23 neonatal deaths and 12 intrauterine fetal demises.

Table 1 summarizes the pre- and postnatal characteristics of the study population. GA at first appearance of oligo- or anhydramnios showed an excellent accuracy in predicting the risk of perinatal mortality with an area under the curve of 0.95 (p < 0.001, 95% CI: 0.92 – 0.98; Figure 1) and with an optimal cut-off at 26 weeks of gestation. Therefore, fetuses with enlarged bladders, but still normal AF at 26 weeks’ gestation were defined as mild LUTO as their risk of perinatal mortality was 8.6% (Table 2 - 3).

Table 1. Antenatal and postnatal characteristics of the study population

<table>
<thead>
<tr>
<th>Antenatal and postnatal characteristics</th>
<th>mean (CI 95%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at diagnosis (weeks)</td>
<td>21 weeks (±8 weeks)</td>
</tr>
<tr>
<td>Early Megacystis (referred &lt;18th week)</td>
<td>97/261 (36%)</td>
</tr>
<tr>
<td>Late Megacystis (referred ≥18th week)</td>
<td>164/261 (63%)</td>
</tr>
<tr>
<td>Bladder volume (cm³)</td>
<td>37 (±93)</td>
</tr>
<tr>
<td>Longitudinal bladder diameter (mm)</td>
<td>41 (±22)</td>
</tr>
<tr>
<td>Left antero-posterior pelvic diameter (mm)</td>
<td>9.8 (7-10)</td>
</tr>
<tr>
<td>Right antero-posterior pelvic diameter (mm)</td>
<td>9.9 (8-11)</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>160/205 (78%)</td>
</tr>
<tr>
<td>Ureteral size (mm)</td>
<td>5 (±6)</td>
</tr>
<tr>
<td>Oligo- or anhydramnios during pregnancy</td>
<td>130/261 (50%)</td>
</tr>
<tr>
<td>GA at first oligohydramnios (weeks)</td>
<td>29 (±9)</td>
</tr>
<tr>
<td>Intrauterine fetal death</td>
<td>12/151 (8%)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>23/151 (15%)</td>
</tr>
<tr>
<td>Alive</td>
<td>116/151 (77%)</td>
</tr>
<tr>
<td>Birth weight (gr)</td>
<td>2680 (±1958)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (CI 95%) or median (range); GA, gestational age.
Figure 1. Receiver operating characteristic (ROC) curve of Gestational age at first appearance of oligohydramnios for the prediction of perinatal mortality.

Oligohydramnios was defined by an amniotic fluid index (AFI) lower than 5 cm or maximum vertical pocket lower than 2 cm. In fetuses referred at an earlier gestational age (<26 weeks’ gestation), the accuracy of the first ultrasound scan in predicting perinatal mortality was tested by univariate and multivariate analysis (Table 4). Multivariate analysis with backward stepwise strategy revealed that urinary bladder volume (BV) is the best single predictor of perinatal mortality and that inclusion of other parameters, such as ureteral size, hydronephrosis and abnormal renal cortical appearance, does not improve predictive accuracy.

Table 2. Staging of LUTO based on bladder volume at referral and GA at first appearance of oligo- or anhydramnios.

<table>
<thead>
<tr>
<th>Definition</th>
<th>glacier</th>
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</thead>
<tbody>
<tr>
<td>Severe LUTO</td>
<td>Bladder volume ≥ 5.4 cm³ and/or oligo-anhydramnios before 20 weeks</td>
</tr>
<tr>
<td>Moderate LUTO</td>
<td>Bladder volume &lt; 5.4 cm³ and/or Normal AF at 20 weeks</td>
</tr>
<tr>
<td>Mild LUTO</td>
<td>Normal AF at 26 weeks</td>
</tr>
</tbody>
</table>
In fetuses referred before the 26th week of gestation, ROC curve analysis indicated as optimal cut-off for the prediction of an adverse outcome a BV of 5.4 cm³ at 20 weeks' gestation. Therefore, fetuses with a BV ≥ 5.4 cm³ or an abnormal AF before 20 weeks' gestation were defined as severe LUTO and those with BV < 5.4 cm³ and still normal AF at the 20 weeks' scan were defined as moderate LUTO (Table 2). Perinatal mortality in fetuses with severe and moderate LUTO was 55% (18/33) and 26% (10/38), respectively (Table 3).

Table 3. Survival rate, mean GA at oligo- or anhydramnios and abnormal renal cortical appearance by LUTO stage.

<table>
<thead>
<tr>
<th>Perinatal mortality</th>
<th>GA at 1° evidence oligohydramnios (mean ± SD)</th>
<th>ARCA</th>
<th>Mean eGFR ml/min/1.73 m²</th>
<th>eGFR &lt; 30 ml/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe LUTO</td>
<td>54.5% (18/33)</td>
<td>21 ± 8 weeks</td>
<td>79%</td>
<td>65 ± 47</td>
</tr>
<tr>
<td>Moderate LUTO</td>
<td>26.3% (10/38)</td>
<td>29 ± 8 weeks</td>
<td>68%</td>
<td>57 ± 44</td>
</tr>
<tr>
<td>Mild LUTO</td>
<td>8.6% (6/70)</td>
<td>35 ± 4 weeks</td>
<td>34%</td>
<td>87 ± 43</td>
</tr>
</tbody>
</table>

ARCA, abnormal renal cortical appearance; eGFR, estimated glomerular filtration rate.

Table 4. Univariate analysis for the prediction of perinatal mortality in fetuses referred before the 26th week of gestation.

<table>
<thead>
<tr>
<th></th>
<th>OR (CI 5-95%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydronephrosis</td>
<td>0.9 (0.83-1.52)</td>
<td>1.4</td>
</tr>
<tr>
<td>Ureteral size</td>
<td>1.1 (0.98-1.43)</td>
<td>1.3</td>
</tr>
<tr>
<td>Bladder volume</td>
<td>0.98 (0.97-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Abnormal renal cortical appearance</td>
<td>0.1 (0.04-0.42)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Based on these results, a staging system capable of stratifying LUTO cases according to their risk of perinatal mortality and postnatal renal function was developed (Figure 2). The prognosis worsens progressively, in terms of perinatal mortality and risk of severely impaired postnatal renal function (eGFR < 30 ml/min/1.73 m²), according to the BV at diagnosis and the GA at first appearance of oligohydramnios, from mild to moderate and to severe LUTO stage (Table 3 - Figure 2). An additional category of cases with ineluctable perinatal mortality was identified: all fetuses with BV > 200 cm³ and oligohydramnios before 18 weeks had an adverse prognosis.
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Figure 2. Kaplan-Meier curve for the overall survival according to the LUTO stage: cumulative survival on the y axis and gestational age on the x axis.

Discussion

This study shows that in fetuses with LUTO, a staging system taking into account the GA at first evidence of oligo- or anhydramnios and bladder volume can reliably predict survival and postnatal renal function. Fetuses classified as having a mild form of LUTO had approximately a 90% chance of survival with a good renal function in the majority of cases, whereas in moderate and severe LUTO stages, perinatal survival was reduced to 75% and 45%, respectively. In the survivors, severe renal dysfunction (eGFR < 30 ml/min/1.73 m²) requiring renal transplant or dialysis in the first year of life was observed in 31% and 44% of cases, respectively.

The natural history of LUTO is highly variable, and reliable criteria to predict whether renal function and AF volume will be preserved throughout pregnancy or not are still missing (16). This study shows that the GA at the first evidence of oligohydramnios can accurately predict the risk of perinatal mortality and, as expected, the earlier oligohydramnios occurs, the poorer the outcome (17). The optimal threshold for predicting adverse outcome is 26 weeks of gestation at first evidence of oligo- or anhydramnios. This GA corresponds to the end of the canalicular phase (18)(17), a crucial period for the development of the anatomical structures needed for an intact gas-exchange function of the fetal lungs (19) (17). Previous studies have reported similar results showing that the risk of perinatal death is more than 80% in second-trimester oligohydramnios with onset before 25 weeks’ gestation.
and persisting for more than 14 days (20)(21)(22)(23). Conversely, if AF is still within normal ranges at 26 weeks, there is a 90% chance of survival with an acceptable postnatal renal function in more than 90% of cases (mean eGFR: 87 ml/min/1.73 m²). These results confirm the findings reported by the North American Fetal Therapy Network (7).

The best single predictor of adverse outcome in LUTO referred before the 26th week of gestation was the bladder size at diagnosis. In fact, we can assume that the larger the bladder, the more severe the obstruction and therefore the higher the chance of developing oligo- or anhydramnios earlier during pregnancy. This finding is in agreement with a few other studies, stressing the importance of bladder measurement for fine-tuning the prenatal diagnosis and the prediction of prognosis in LUTO (24)(25). Unfortunately, the lack of accurate normal ranges for fetal bladder size and urine production in the second and third trimester of pregnancy still lead to inaccuracies with both over- as well as under-diagnoses of enlarged bladders, especially in fetuses with borderline enlargements. However, as suggested by Lee et al., in the future fetal urine production assessment may provide a superior alternative for diagnosing oligohydramnios (26), as the AFI and the SDP measurement are often poor predictors of the actual AF volume (27).

The vesico-amniotic shunt (VAS) placement has demonstrated to improve perinatal survival (10), with an unclear role for preventing renal damage (11), and is therefore typically proposed in fetuses with high risk of perinatal mortality. However, Morris et al showed that in this population the chance of surviving with normal renal function is very low irrespective of whether or not the VAS is placed (10). We believe that the lack of a robust staging system and consistent eligibility criteria has represented major limitations for evaluating the real effectiveness of VAS, that is likely to change according to the LUTO severity (28). This study suggests that offering VAS to cases with early oligohydramnios is at least questionable, as these fetuses have already a high chance of mortality and compromised renal function (10) (29). Future studies are needed to clarify the role of fetal intervention in terms of perinatal survival and postnatal renal function according to each LUTO stage.

Recently, Ruano et al. proposed a management protocol with a classification of LUTO severity based on AF amount and fetal renal function, that was purely inferred from antenatal parameters such as absence of bilateral renal dysplasia, renal cysts and urinary biochemistry, without analyzing postnatal renal function and urological sequelae. Their retrospective study included 25 fetuses with LUTO, 14 of which treated with VAS. In light of the small sample size, the antenatal predictors of survival were analyzed by using a Bayesian methodology.

Similarly, we aimed at stratifying the risk of perinatal mortality by including a much larger population and only managed conservatively during pregnancy. Another strength of our study is that LUTO was defined by a set of antenatal criteria, that we already elaborated in previous studies, rather than on less predictive and non-objective criteria, prone to produce
high rate of false-positive cases (2)(12). This approach is also more suitable than relying upon the evidence of LUTO at pathological examination on terminated or demised fetuses or on the postnatal assessment on surviving infants.

A potential limitation of our study is that we excluded the cases with terminations of pregnancy as no renal function parameters were available. In order to obviate this, we have evaluated retrospectively the severity of LUTO in each single TOP and found that 77% would have been classified as severe or moderate, whereas the remaining 23% would have been milder LUTO cases, where parents opted for termination of pregnancy in view of the uncertain prognosis. This distribution is similar to that of the included cases of this study.

To conclude, this study proposes a staging system based on urinary bladder volume and GA at first evidence of oligohydramnios to reliably triage fetuses with LUTO and predict the risk of perinatal mortality and adverse postnatal outcome. We believe that this classification could help in counseling parents on the prognosis and identifying the few cases eligible for a meaningful antenatal management.
References

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LUTO staging system