Prediction model of postnatal renal function in fetuses with lower urinary tract obstruction (LUTO)—Development and internal validation

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Abstract
Objective: To develop a prediction model of postnatal renal function in fetuses with lower urinary tract obstruction (LUTO) based on fetal ultrasound parameters and amniotic fluid volume.

Methods: Retrospective nationwide cohort study of fetuses with postnatally confirmed LUTO and known eGFR. Fetuses treated with fetal interventions such as vesico-amniotic shunting or cystoscopy were excluded. Logistic regression analysis was used to identify prognostic ultrasound variables with respect to renal outcome following multiple imputation of missing data. On the basis of these fetal renal parameters and amniotic fluid volume, a model was developed to predict postnatal renal function in fetuses with LUTO. The main study outcome was an eGFR less than 60 mL/min * 1.73 m² based on the creatinine nadir during the first year following diagnosis. Model performance was evaluated by receiver operator characteristic (ROC) curve analysis, calibration plots, and bootstrapping.

Results: Hundred one fetuses with a confirmed diagnosis of LUTO were included, eGFR less than 60 was observed in 40 (39.6%) of them. Variables predicting an eGFR less than 60 mL/min * 1.73m² included the following sonographic parameters: hyperechogenicity of the renal cortex and abnormal amniotic fluid volume.
1 | INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) refer to a broad spectrum of renal malformations, which originate in defects in embryonic kidney development. In the spectrum of major birth defects, congenital anomalies of the kidneys and urinary tract account for 20% to 30% of all congenital malformations, with a prevalence of 3 to 6 per 1000 births. The most common abnormality is ureteropelvic junction obstruction (UPJ), accounting for 20% to 30% of the CAKUT spectrum. But the spectrum ranges from transient hydrenephrosis to bilateral renal agenesis and is the leading cause of end-stage kidney disease (ESKD), accounting for 41% of cases. Other underlying pathology are urethral atresia or stenosis and prune belly syndrome. Although the combination of prenatal signs such as oligohydramnios, a distended thick-walled bladder, a keyhole sign, parenchymal abnormalities, and hydrenephrosis can predict LUTO in 87% of cases. Other conditions such as vesico-ureteral reflux (VUR) (24.5%), cloacal malformations (18.9%), hydrenephrosis (11.3%), or no bladder abnormality after birth (18.9%) can erroneously be classified as LUTO and give rise to false positive prenatal diagnosis. LUTO itself is a complex condition associated with a high perinatal mortality rate because of the ensuing lung hypoplasia and end-stage renal failure. In the setting of LUTO, it is extremely challenging to predict prenatally the exact postnatal renal and pulmonary function, the degree of persistent bladder dysfunction and of hypertensive disease, before undertaking an attempt to alleviate the primary cause of the urethral obstruction. The severity of LUTO, in terms of perinatal mortality and postnatal outcome, is usually estimated on the basis of amniotic fluid volume, renal cortical appearance, degree of hydrenephrosis, and eventually on the biochemical analysis of fetal serum or fetal urine. Although the majority of these parameter have demonstrated good accuracy in predicting the outcome of LUTO, they have never been combined in a multivariate analysis to calculate the individual risk of postnatally compromised renal function.

The aim of this study was to develop a model based on fetal renal ultrasound parameters and amniotic fluid volume able to predict postnatal renal function in fetus with LUTO.

2 | METHODS

This study is part of a multicenter study performed in eight university medical centers in the Netherlands. We present data from the Erasmus Medical Center, Academic Medical Center (AMC), and the University Medical Center of Maastricht (MUMC+) for cases of LUTO from a cohort of births between 2000 and 2015. From the University Medical Center Groningen (UMCG) and Radboud University Medical Center (RadboudUMC) between 2004 to 2015, and from 2007 to 2014 in the remaining centers (VU Medical Center, Amsterdam (VUmc), Leiden University Medical Center (LUMC), University Medical Center Utrecht (UMCU)).

After referral to one of the University Fetal Medicine Units in the Netherlands, all fetus with a prenatally suspected LUTO, and with a postnatally confirmed diagnosis of LUTO (by cystoscopy and MCUG) and a known eGFR were included in the final cohort. Cases with neonatal death due to lung hypoplasia and confirmed LUTO diagnoses but without a known eGFR were classified as kidney failure for methodological accuracy. Cases with a false positive diagnosis of LUTO (ie, vesico-ureteric reflux and neurogenic bladder) and LUTO cases treated with fetal interventions as vesico-amiotic shunts (VAS) or fetal cystoscopy were excluded. The collected data were used to develop a model to predict the estimated glomerular filtration rate (eGFR) postnatally after confirmation of the diagnosis of LUTO. The eGFR was calculated using the Schwartz formula, considering the length of the infant and the creatinine nadir in the first year of diagnosis. Creatinine nadir was defined as the lowest creatinine during the first year following diagnosis.

This study was approved by the Medical Ethics committee of the University Medical Center Groningen (METc 2015/445).

3 | BUILDING THE PREDICTION MODEL

According to the 2012 Chronic Kidney Disease (CKD) guideline “Improving Global Outcomes (KDIGO),” CKD is defined as abnormalities of kidney structure or function present for more than 3 months, with implications for health. Criteria for CKD include: (a) markers of kidney damage (one or more) include albuminuria, urine sediment abnormalities, electrolyte, and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected...
by imaging, history of kidney transplantation; and (b) decreased GFR: eGFR < 60 mL/min * 1.73 m² (categories G3A-G5).

In general, the definition of CKD in adults applies to children (from birth to 18 years) with the following exceptions or allowances:

- the criteria for duration more than 3 months does not apply to newborns or infants less than or equal to 3 months of age.
- The criteria of a GFR less than 60 mL/min * 1.73 m² does not apply to children less than 2 years of age in whom an age-appropriate value should be applied.
- A urinary total protein or albumin excretion rate above the normal value for age may be substituted for albuminuria more than or equal to 30 mg per 24 hours.
- All electrolyte abnormalities are to be defined in light of age normative values.

Taking into account that normal GFR in newborns is less than 60 mL/min * 1.73 m², it is not until approximately 2 years of age that one expects to see body surface area (BSA) adjusted GFR values comparable with those seen in adults. Different reference values for preterm, neonatal term, and infants exists. Reference values of Haycock et al for neonatal term infants were used in the model. Implying an eGFR more than 60 mL/min * 1.73 m² calculated by Schwartz formula is normal for a term born neonate of 2 weeks of age.

Cases with eGFR less than 60 mL/min * 1.73 m² were defined as having a compromised renal function and used as the primary end-point of this study. The guideline classifies CKD into category 3a, mildly to moderately decreased kidney function (eGFR 59-45 mL/min * 1.73 m²); category 3b, moderately to severely decreased kidney function (eGFR 44-30 mL/min * 1.73 m²); category 4, severely decreased kidney function (eGFR 29-15 mL/min * 1.73 m²); and category 5, kidney failure (eGFR less than 15 mL/min * 1.73 m² and dialysis).

On the basis of the current literature and ultrasound parameters derived from the database, we identified a number of predictive variables. The candidate parameters were as follows:

- Gestational age at diagnosis (weeks)
- Bladder longitudinal diameter (mm)
- Renal cortical appearance (hyper echogenicity of the renal cortex)
- Renal anteroposterior diameter (mm)
- Renal pelvis anteroposterior diameter (mm)
- Amniotic fluid volume (single deepest pocket [SDP])
- Presence of a keyhole sign
- Bladder wall thickness (mm)
- Presence of a thickened bladder wall

Hyper echogenicity of the renal cortex was defined as echogenicity greater than liver and as echogenic as bone.

There were no missing data for the end-point of the study, the eGFR. Ideally, all other candidate parameters should be known in order to be able to build the model. Overall, more than 75% of values were available across all variables, which is a well-accepted percentage for imputation. On this basis, we performed multiple imputation according to current practice for prediction models. Imputation was performed using SPSS statistics 23 (SPSS Inc Chicago, Illinois). Predictive mean matching was applied and twenty imputed datasets were generated.

### Statistical analysis

Using the imputed multiple dataset, logistic regression was performed to predict occurrence of the primary end-point. For both dichotomous and continuous variables, univariable pooled odds ratios and 95% confidence intervals (CI), as well as P values, were calculated. All predictive variables that had P < .157 in the univariable analysis were considered as potential candidates for inclusion in the multivariable prediction model. Multivariable logistic regression with manual backward stepwise selection was used to create the final model using the same cut-off P value.

To evaluate the discriminative performance of the model, the receiver operator characteristic (ROC) curve was plotted and the area under the curve (AUC or c-statistic) was calculated using the mean predicted probabilities across the imputations. This statistic ranges from 0.5 (no discrimination) to 1 (perfect discrimination).

For the calibration of the model, correspondence between the predicted probabilities and the observed proportions was plotted in a calibration plot. Because of the low number of cases and the limited number of discrete predicted probabilities corresponding with unique combinations of values of the categorical predictor variables, five subgroups were created based on the distribution of the predicted probabilities instead of the recommended 10 subgroups based on deciles of predicted probability. The fit of the logistic regression model was also assessed based on the Hosmer-Lemeshow goodness of fit test. This
test is performed on a cross-table of two columns (the observed dichotomous outcome) by 10 rows (deciles of the predicted probability). A high P value is favorable since it indicates that the identification of cases depends on the predicted probability. Internal validation was performed by bootstrap replication for each of the imputed datasets to assess the extent of overfitting of the model.

All analyses were performed using IBM SPSS Statistics version 23 (Chicago, Illinois).

## RESULTS

During the study period, LUTO was antenatally suspected and confirmed at postmortem or postnatal examination in 222 cases. Of these, fetal demise occurred in 12 cases and in 71 cases, the pregnancy was terminated. Neonatal death occurred in 32 cases, among which lung hypoplasia and extreme prematurity were causes of death without a known eGFR. Twelve cases were excluded, either because of loss to follow up or treatment by vesico-anniotic shunting (VAS n = 6).

In total, 95 fetus with confirmed diagnoses of LUTO and known postnatal eGFR and six cases with neonatal death due to lung hypoplasia and confirmed diagnoses of LUTO with unknown eGFR, the latter classified as kidney failure (CKD category 5), met our criteria for analysis. The description of the total population of fetuses with prenatally diagnosed megacystis, retrieved from the eight university medical centers, was described previously by Fontanella et al.17

Descriptive characteristics of the patients used in our model are presented in Table 1. The eGFR was based on a creatinine nadir at a mean duration of 11 months. There were 61 (60.4%) cases with normal renal function, nine (8.9%) with mild to moderately decreased renal function, nine (8.9%) cases with moderately to severely impaired renal function, eight (7.9%) with severely decreased renal function, and 14 (13.9%) cases with renal failure according to the KDIGO 2012 CKD guideline.12 In total, seven infants were in need of a kidney transplantation after a mean 69 months of age (min-max 34-131 mo) with a mean eGFR of 15.3 mL/min * 1.73 m² and mean creatinine nadir of 226 μmol/L. Three infants were in need of peritoneal dialysis, with a mean eGFR of 11.3 mL/min * 1.73 m² and mean creatinine nadir of 320 μmol/L. Six neonates died because of lung hypoplasia in the neonatal period, without a known eGFR.

Univariable analysis showed that the presence of a keyhole sign, hyper echogenicity of the renal cortex, and abnormal amniotic fluid volume were associated with a higher chance of compromised renal function (eGFR less than 60 mL/min * 1.73 m²) (P > .157, Table 2). Two of the three predictors qualified for inclusion in the final multivariable logistic regression model (Table 3).

The developed model had a fair discriminative capacity with a c-statistic of 0.699 (95% CI, 0.591-0.807), and after bootstrap replication, the mean c-statistic was 0.662 (AUC varied from 0.631-0.712) (Figure 1). The estimated overfitting was calculated to be 2.3%. The model was well-calibrated, as indicated by the Hosmer-Lemeshow goodness-of-fit test (average P value 0.744) and by the calibration plot (Figure 2). The observed proportion in the data and the expected

### TABLE 1 Descriptive characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 101(%)</th>
<th>Mean</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at diagnosis (weeks)</td>
<td>25</td>
<td>12-42</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>37</td>
<td>32-42</td>
<td></td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3233</td>
<td>1490-4925</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>99 (98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min * 1.73 m²)</td>
<td>78.1</td>
<td>1.74-162</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>44 (43.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-60</td>
<td>17 (16.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-30</td>
<td>18 (17.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-15</td>
<td>8 (7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>14 (13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine nadir (μmol/L)</td>
<td>68.13</td>
<td>13-785</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2 Univariable logistic regression of factors predicting postnatal eGFR after confirmed LUTO diagnosis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.971</td>
<td>0.917-1.027</td>
<td>.305</td>
</tr>
<tr>
<td>Bladder dimensions</td>
<td>0.998</td>
<td>0.971-1.025</td>
<td>.865</td>
</tr>
<tr>
<td>Bladder wall thickness (mm)</td>
<td>1.037</td>
<td>0.937-1.147</td>
<td>.477</td>
</tr>
<tr>
<td>Bladder wall thickened</td>
<td>0.431</td>
<td>0.111-1.665</td>
<td>.221</td>
</tr>
<tr>
<td>Keyhole sign</td>
<td>2.645</td>
<td>0.800-8.333</td>
<td>.111</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>2.647</td>
<td>1.041-6.734</td>
<td>.041</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>0.698</td>
<td>0.197-2.482</td>
<td>.579</td>
</tr>
<tr>
<td>AF (SDP &gt; 3 cm, n = 67)</td>
<td>1 (ref)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AF (SDP &lt; 3 cm, n = 18)</td>
<td>2.074</td>
<td>0.705-6.099</td>
<td>.185</td>
</tr>
<tr>
<td>AF (anhydramnion, n = 7)</td>
<td>12.11</td>
<td>1.284-117.074</td>
<td>.029</td>
</tr>
<tr>
<td>AF (polihydramnion, SDP &gt; 3 cm, n = 3)</td>
<td>1.366</td>
<td>0.130-14.374</td>
<td>.795</td>
</tr>
<tr>
<td>Kidney diameter (mm)</td>
<td>0.990</td>
<td>0.936-1.047</td>
<td>.719</td>
</tr>
</tbody>
</table>

Note. Bladderwall thickness, continuous variable in mm; Bladderwall thickness, dichotomous variable (yes/no); AF, amniotic fluid; SDP, single deepest pocket; Kidney diameter, antero-posterior diameter

<sup>a</sup>Gestational age at diagnosis
The proportion as predicted by the logistic model corresponded reasonably well. Ideally, all the points fall on the diagonal line. For the lowest quintiles, the calibration was not optimal.

The final equation for the prediction model was: \[
\text{logit (logarithm of the odds) [low eGFR] = -1.336 + [0.889 \times \text{indicator for abnormal cortical appearance}] + [0.897 \times \text{indicator for oligohydramnion}] + [2.594 \times \text{indicator for anhydramnion}] + [0.813 \times \text{indicator for polyhydramnion}].
\]

Table 4 shows an example of calculated probabilities of eGFR less than 60 mL/min * 1.73 m² in fetus with LUTO for four hypothetical cases based on our prediction model.

### TABLE 3  Multivariable logistic regression analysis for predicting eGFR after confirmed LUTO diagnosis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper echogenicity of renal cortex</td>
<td>2.433</td>
<td>0.934-6.338</td>
<td>0.069</td>
</tr>
<tr>
<td>AF (SDP &gt; 3 cm)</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF (SDP &lt; 3 cm)</td>
<td>2.451</td>
<td>0.863-6.962</td>
<td>0.092</td>
</tr>
<tr>
<td>AF (anhydramnion)</td>
<td>13.389</td>
<td>1.468-122.1</td>
<td>0.021</td>
</tr>
<tr>
<td>AF (polyhydramnion)</td>
<td>2.256</td>
<td>0.215-23.672</td>
<td>0.497</td>
</tr>
</tbody>
</table>

Abbreviations: AF, amniotic fluid; SDP, single deepest pocket.

### TABLE 4  Prediction of eGFR less than 60 mL/min * 1.73 m² for four hypothetical patients

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Case A</th>
<th>Case B</th>
<th>Case C</th>
<th>Case D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperechogenicity of renal cortex</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>AF normal (SDP &gt; 3 cm)</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AF (SDP &lt; 3 cm)</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AF (anhydramnion)</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AF (polyhydramnion)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Predicted probability</td>
<td>89%</td>
<td>61%</td>
<td>39%</td>
<td>21%</td>
</tr>
<tr>
<td>Range in imputations</td>
<td>88-92%</td>
<td>56-68%</td>
<td>36-43%</td>
<td>19-25%</td>
</tr>
</tbody>
</table>

FIGURE 1  Receiver operating characteristic curve (ROC) of the multivariable logistic regression model for predicting eGFR in LUTO based on mean predicted probabilities from all imputations. The area under the curve was 0.699 (95% CI, 0.591-0.807) [Colour figure can be viewed at wileyonlinelibrary.com]

proportion as predicted by the logistic model corresponded reasonably well. Ideally, all the points fall on the diagonal line. For the lowest quintiles, the calibration was not optimal.

The final equation for the prediction model was: \[
\text{logit (logarithm of the odds) [low eGFR] = -1.336 + [0.889 \times \text{indicator for abnormal cortical appearance}] + [0.897 \times \text{indicator for oligohydramnion}] + [2.594 \times \text{indicator for anhydramnion}] + [0.813 \times \text{indicator for polyhydramnion}].
\]

Table 4 shows an example of calculated probabilities of eGFR less than 60 mL/min * 1.73 m² in fetus with LUTO for four hypothetical cases based on our prediction model.

### 5  DISCUSSION

In this study, we propose a model to predict postnatal outcome in infants with prenatally suspected LUTO based on prenatal ultrasound characteristics. The model was developed with the data collected in a national cohort of live born children with a confirmed diagnoses of LUTO and known eGFR. In our analysis of 95 fetus with LUTO and six fetus with LUTO and death due to longhypoplasia, we found that an eGFR less than 60 mL/min * 1.73 m² was associated with sono-graphic hyperechogenicity of the renal cortex and abnormal amniotic fluid volume at initial diagnosis. After model development using multivariable logistic regression analysis, an AUC of 0.699 was calculated.

This is one of the largest series showing the natural history of LUTO without fetal intervention as VAS or fetal cystoscopy. We investigated whether fetuses at increased risk of developing renal failure could be identified from fetal ultrasound parameters, in the attempt to facilitate counseling of parents and decision making on a more individual basis.

We found similar predictors as cortical appearance and abnormal amniotic fluid volume as described in the previous systematic review by Morris et al. From all described ultrasound parameters, cortical appearance had the best predictive value for postnatal renal function with a sensitivity of 0.57 (95% CI, 0.37-0.76), a specificity of 0.84 (95% CI, 0.71-0.94), and an area under the curve 0.78. Despite this fair predictive accuracy, the authors concluded that on the overall
capability of individual antenatal ultrasound parameters to predict postnatal function was unsatisfactory.

To increase the predictive ability of the model, one may argue that we should have incorporated fetal urinalysis. However, there are conflicting data on the diagnostic ability of biochemical analysis of the fetal urine in predicting fetal renal outcome. Furthermore, ultrasound parameters of the fetal kidney and urinary biochemistry are not correlated and should be taken separately into account when making a risk assessment for fetuses with LUTO.

Although incorporation of urinalysis in the model may have contributed to a better risk stratification of fetuses candidate for fetal interventions, unfortunately because of the retrospective nature of this cohort, these results were only available in a minority of cases. Another limitation of our study is the lack of external validation. External validation is a crucial aspect in estimating the applicability of a prognostic model in a population outside the scope where the data were derived from. One could apply the prognostic model on an external population or split the initial data set in a training and validation sample or retrieve data from a different time frame. However, owing to the low incidence of LUTO, the retrospective design of the nationwide study with inevitable missing data and the need for imputation, external validation was not yet possible. It will be of paramount importance to test this prognostic model in another population in the future, especially to assess if it is capable of identifying cases with a good eGFR. This is in fact where the predicted probability may overestimate the observed probability of renal impairment. This is also the subgroup of fetuses amenable to prenatal intervention.

A recently published classification system with selection criteria for eligibility for fetal intervention by Ruano et al, approaches the fetus on an individual basis to provide the current best management. This classification system uses fetal renal ultrasound parameters, amniotic fluid volume, and fetal urinalysis separately. However, an individualized estimate of the postnatal renal function is not attempted. To improve selection of a group of fetuses eligible for prenatal therapy, an approach could be to further refine the information inferred from the ultrasound parameters and diminish the subjectivity of, for instance, assessing hyperechogenicity of the renal cortex. A novel approach that needs investigation could be the use of objective tools, such as a gray-scale histogram to infer the residual renal function. The other remaining challenge is to investigate the best therapeutic modality after risk stratification. Previous studies have compared VAS versus no fetal therapy, or fetal cystoscopy versus no fetal intervention. The aims of the randomized-controlled PLUTO trial were to determine the efficacy and safety of VAS in lower urinary tract obstruction. Unfortunately, the trial was prematurely stopped because of low inclusion rates. Although power for significant results was not achieved, the study suggested a potential benefit for survival in the intervention group (VAS placement) versus the expectant management one. The nonrandomized cohort of Ruano et al confirmed these results showing improvement of the survival rate in the first 6 months in cases of severe LUTO after fetal intervention as VAS or cystoscopy. However, as suggested by the recent review of Nassr et al, including the above mentioned studies, cystoscopy is an alternate method for relieving LUTO and no data are available to compare its effectiveness to the currently gold standard VAS on prevention of renal function impairment or increased survival. However, it must be stressed that in spite of this encouraging short-term results, the degree of renal impairment after 1- to 2-year survival remains uncertain and needs further investigation.

In conclusion, our study has shown that a prediction model incorporating ultrasound parameters such as cortical appearance and abnormal amniotic fluid volume can make a fairly accurate distinction between an eGFR above or below 60 mL/min * 1.73m², considered as the critical cut-off between acceptable and expected poor renal function. Once the predictive ability of the model is validated in another set of data, this tool could be used to provide parents with a tailored counseling and possibly give a better risk stratification of fetuses with LUTO eligible for fetal interventions. Future research is needed to improve the efficacy of renal kidney function predictors and answer the question regarding which therapeutic modality has to be applied in order to preserve and prevent further deterioration of the fetal renal function.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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