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Outcomes in Fetal Lower Urinary Tract Obstruction: Analysis of Fetal Urinary Biochemistry and Ultrasound Features in Fetuses with and without Additional Upper Renal Tract Involvement

Bijoya Mukherjee[1], Urvashi Chhikara[1], Dr Sujit Chowdhury[2], Akshatha Sharma[1], Anita Kaul[1*]

Abstract

Objective: We wished to assess if fetal urinary biochemistry assessment can improve the prediction of postnatal renal outcomes over traditional ultrasound features of renal cortical appearance, shape of bladder and amniotic fluid volume in fetuses with no upper renal tract involvement in antenatally diagnosed LUTO.

Methods: Retrospective analysis of data was done for 58 cases of LUTO over a period of 10 years. All cases of live births were subdivided into two groups: fetuses with upper renal tract involvement (hydronephrosis) and those with none. The outcome measures included stillbirths, neonatal deaths, live births with poor renal outcome (serum creatinine >60umol/L at minimum 2 years age) and live births with good long term renal outcome (serum creatinine <60umol/L at minimum 2 years age). Statistical analysis was done to determine the diagnostic accuracy of B2 microglobulin and ultrasound features in predicting postnatal outcome in both the groups.

Results: High B2 microglobulin was a good predictor of poor postnatal outcome irrespective of presence or absence of upper renal tract involvement. Among the ultrasound markers renal dysplasia or presence of renal cortical cysts faired as a good predictor (AUC 0.706) while morphology of bladder (floppy bladder) and amniotic fluid volume had low predictive accuracy (AUC 0.553 and AUC 0.595 respectively). Thus addition of B2 microglobulin in cases of LUTO improves the predictive accuracy of poor renal function, even in cases where there is no upper renal tract involvement and we generally expect a good postnatal outcome.

Conclusion: Inclusion of B2 microglobulin in antenatally detected cases of LUTO can improve the accuracy of expected postnatal outcome, and hence combination of ultrasound and B2 microglobulin should be used in all antenatally detected cases of LUTO.

Keywords: Bladder; Urinary tract obstruction; Fetal; B2 microglobulin; Ultrasound

Abbreviations: LUTO: Lower Urinary Tract Obstruction; HDN: Hydronephrosis

Introduction

Fetal Lower urinary tract obstruction (LUTO) is a rare disorder characterized by obstruction in the fetal urethra, resulting in a dilated bladder and progressive urinary tract dilatation. The acute obstruction in urinary flow causes damage to glomeruli, thereby causing deterioration of kidney

Affiliation:

[1]Apollo Centre for Fetal Medicine, Indrapastha Apollo Hospitals, NH-19, New Delhi, India

[2]Department of Pediatric Surgery, Indraprastha Apollo Hospital, New Delhi, India

***Corresponding author:**

Anita Kaul, Apollo Centre for Fetal Medicine, Indrapastha Apollo Hospitals, NH-19, New Delhi, India

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function [1]. The reduction in amniotic fluid volume causes pulmonary hypoplasia and contributing to neonatal mortality and morbidity. Long-term complications like chronic kidney disease end-stage renal disease may develop in survivors of LUTO, necessitating dialysis and renal replacement therapy.

Postnatal prediction of the severity of LUTO is challenging. Several prediction models have been used to determine the degree of renal compromise postnatally. Ultrasound features of renal cortical appearance, shape of bladder and amniotic fluid volume, individually and when combined, have been utilized to determine postnatal renal function [2,3]. The presence of oligohydramnios or anhydramnios has been predicted to have a poor postnatal outcome; however, normal amniotic fluid volume does not suggest a similar predictive value [4]. Biochemical parameters, mainly fetal urinary B2 microglobulin, have been assessed to predict long-term renal outcomes in obstructive uropathies [5], but as this involves an invasive procedure, parents tend to decline fetal urinary biochemistry testing. Through this study we tried to assess if B2 microglobulin can be considered an useful marker in prediction of postnatal renal outcomes over traditional ultrasound features of renal cortical appearance, shape of bladder and amniotic fluid volume in fetuses with no upper renal tract involvement in antenatally diagnosed LUTO.

Materials and Methods

This was a retrospective analysis of antenatally diagnosed cases of LUTO from 2013- 2023 at Apollo Centre for Fetal Medicine and Department of Pediatric surgery at Indrapastha Apollo Hospitals. LUTO is defined as presence of megacystis (bladder diameter >7mm) in 1st trimester and enlarged bladder failing to empty over 45 mins in 2nd/3rd trimester. Oligohydramnios was defined was amniotic fluid volume <5th centile for gestational age. Good postnatal renal outcome was defined as serum creatinine <60umol/L at 2 years of age. Neonatal deaths and live birth with postnatal serum creatinine>60umol/L was taken as poor postnatal renal outcome. Additional ultrasound features taken as predictors of postnatal renal outcome included echogenic kidneys, dysplastic kidneys or presence of renal cysts, and reduced amniotic fluid volume. High B2 microglobulin was defined as more than 5ng/mL in the last sample of vesicocentesis [5]. B2 microglobulin was measured on Immunoturbidimetry, AU400 Chemistry Analyzer.

The following data were retreived from obstetric database (Astraia Gm bH: gestational age at diagnosis, echogenicity of kidneys, presence of renal cysts or dysplasia, shape of bladder at presentation, amniotic fluid volume and any associated abnormalities. They were followed monthly by serial ultrasound scans to check for progression. In those with any of the additional ultrasound parameters or last B2 value greater than 5ng/mL were called at interval of 2 weeks. Decision for delivery was dependent on severity of clinical findings. All were offered biochemical marker (urinary Beta 2 microglobulin) by vesicocentesis and its associated risks were conveyed to the parents. Those who accepted it were followed up with three serial B2 microglobulin at a minimum of 48 hours interval. Those who declined testing were already inclined towards termination or were unwilling to follow up at serial intervals.

The perinatal outcomes included - stillbirths, neonatal deaths (NND), live births with good long term renal outcome (serum creatinine <60umol/L at minimum 2 years age) and live births with poor post-natal outcome (serum creatinine >60umol/L at minimum 2 years age).

All live births were divided into two groups Group A: those who had no upper renal tract involvement (hydronephrosis) and Group B: those who had upper renal tract involvement (hydronephrosis). The comparison of the outcome measures was done for both the groups.

Statistical analysis

Demographic characteristics for Group A and Group B were expressed as means for continuous data. Comparison of the groups was done by Student's t-test. Chi-square or Fisher's exact tests were used to analysis postnatal outcome of isolated LUTO cases. P value < 0.05 was considered as significant. Comparison of performance of screening for postnatal outcome based on ultrasound features and B2 microglobulin analysis in both the groups was determined using ROC curves. SPSS Version 23 were used for the analysis.

Ethical clearance for this study was taken from the Institutional Ethics Committee of Indrapastha Apollo Hospital.

Results

We have described the population flowchart in Figure 1. In our study period, 58 cases were diagnosed antenatally as LUTO. We had excluded 2 cases (who were lost to follow up) and 5 cases having associated anomalies (myelomeningocele, microcolon megacystis, ambiguous genitalia, ileal atresia and umbilical cord cyst). There were no cases of multiple pregnancies.

The demographic parameters for both the groups are described in Table 1. The parameters were comparable in both the groups.

The postnatal outcome of 51 cases has been described in Table 2. 16 cases underwent medical termination of pregnancy. Out of the rest 35 cases, NND occurred in 8 (22.8%) cases. 25 cases (71.4%) survived out of which 24 cases (68.5%) had good kidney function at minimum 2 years of age and only 1 case (2.8%) had poor outcome in long term.

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Mukherjee B, et al., J Pediatr Perinatol Child Health 2024
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Postnatal surgical intervention was done in 13 cases (37.1%). Good long term renal outcome was in 10/13 cases (76.9%) and poor long-term outcome was in 3/13 cases (23.1%) post-surgery.

In Group A, 5 cases were followed up with ultrasound only as they declined B2 microglobulin assessment. Low AFI could predict 100% of cases of poor outcome, however even with normal AFI 50% of cases had a bad prognosis. Floppy bladder was present in 50% of cases of poor outcome. Out of 3 cases who accepted B2 microglobulin assessment, 100% cases had high B2 levels and a poor prognosis. This is depicted in Tables 4 and 5.

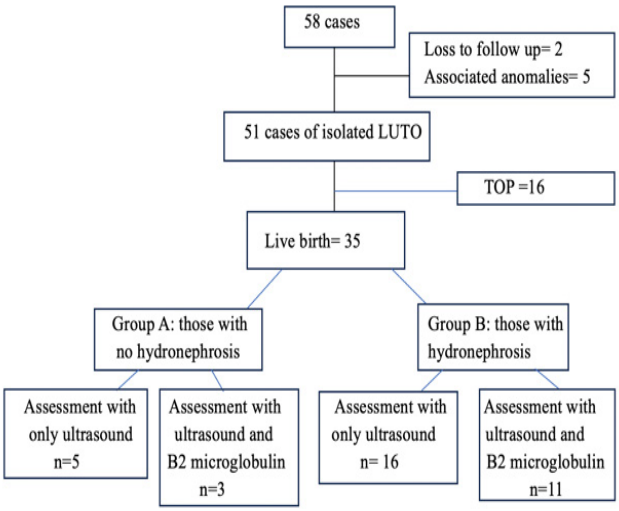

Figure 1: Flowchart of patients with antenatally diagnosed LUTO in the study period.

Table 1: Demographic characteristics of isolated LUTO cases.

Parameters	Group A (n=8)	Group B (n=27)	p value
Mean maternal age	32.11+4.26	33.83+5.54	0.26
Mean maternal BMI	29.30+3.10	29.42+2.87	0.907
GA at diagnosis	25.04+6.83 weeks	25.83+4.09 weeks	0.715
GA at delivery	36.60+1.98 weeks	35.17+1.27 weeks	0.026
Birth weight	2.76+0.54 kg	2.53+0.17 kg	0.17

Table 2: Postnatal outcome of isolated LUTO cases.

Outcome	Group A(n=8)	Group B(n=27)
Stillbirth/ IUD	0	2/27 (7.4%)
NND	2/8 (25%)	6/27 (22.2%)
Livebirth	6/8 (75%)	19/27 (70.3%)
Survivors with poor renal function	0	1/27 (3.7%)
Survivors with good long-term outcome	6/8 (75%)	18/27 (66.6%)
Surgical intervention	4/8 (50%)	9/27(33.3%)

In Group B, 16 cases declined B2 microglobulin assessment and was followed up with ultrasound markers. 66.6% cases had poor outcome due to low AFI, however in normal AFI 47.5% cases also had a poor prognosis. 40% of cases of floppy bladder had a poor prognosis, however even 31.8% of cases of normal bladder ended up in a bad outcome. Hence, neither AFI nor shape of bladder at presentation is a very reliable indicator of the severity of the condition. On the other hand, presence of echogenic kidneys, renal cortical cysts or renal dysplasia did predict 75% cases of poor outcome. This is depicted in Table 6.

In Group B, out of 9 cases who accepted fetal B2 microglobulin assessment, the severity of poor prognosis was predicted by high B2 microglobulin levels in 85.7% cases. Both cases of normal B2 microglobulin levels could predict a normal outcome. This is depicted in Table 7.

Comparing the diagnostic accuracy of the parameters in predicting severity of antenatally diagnosed LUTO, B2 microglobulin has 100% sensitivity with 66% specificity. Among the ultrasound parameters abnormality of renal parenchyma has 64.3% sensitivity with 76.9% specificity (AUC 0.706). This is depicted in Table 8 and Figure 4. The predictive accuracy of AFI and floppy bladder were low (AUC 0.595 and AUC 0.533 respectively), as depicted in Figure 2 and Figure 3.

Table 3: Postnatal outcomes according to presence or absence of upper renal tract involvement.

	Poor outcome n (%)	Good outcome n (%)	P value
No HDN (n=8)	2 (25%)	6 (75%)	0.6
HDN present (n=27)	9 (33.3%)	18 (66.6%)	
Total	11	24	

Table 4: No HDN (n=8).

	Poor outcome n (%)	Good outcome n (%)	P value
Low AFI (n=2)	2 (100%)	0	0.2
Normal AFI (n=6)	3 (50%)	3 (50%)	
Total	5	3	
Floppy Bladder	1(50%)	1 (50%)	0.3
Normal Bladder	1 (16.6%)	5 (83.3%)	
	2	6	

Table 5: No HDN (n=8).

B2 accepted n=3, B2 not accepted n=5			
	Poor outcome n (%)	Good outcome n (%)	P value
High B2 (n=3)	3 (100%)	0	Cannot be calculated due to small numbers
Normal B2 (n=0)	0	0	
Total	3	0	

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Mukherjee B, et al., J Pediatr Perinatol Child Health 2024
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Table 6: HDN present (n=27)

	Poor outcome n (%)	Good outcome n (%)	P value
Low AFI (n=6)	4 (66.6%)	2 (33.3%)	0.3
Normal AFI (n=21)	10 (47.6%)	11 (52.3%)	
Total	14	13	
Renal dysplasia present (n=12)	9 (75%)	3 (25%)	0.03
No renal dysplasia (n= 15)	5 (33%)	10 (66%)	
Total	14	13	
Floppy bladder	2 (40%)	3(60%)	0.7
Normal bladder	7 (31.8%)	15 (83.3%)	
Total	9	18	

Table 7: HDN present (n=27)

B2 accepted n= 9, B2 not accepted n= 16			
	Poor outcome n (%)	Good outcome n (%)	P value
High B2 (n=7)	6 (85.7%)	1 (14.2%)	0.02
Normal b2 (n=2)	0	2 (100%)	
Total	6	3	

Table 8: Diagnostic accuracy of the parameters in predicting poor renal outcome

	Sensitivity	Specificity	PPV	NPV
AFI	0.316	0.875	0.75	0.518
Renal dysplasia	0.643	0.769	0.75	0.666
Floppy bladder	0.272	0.833	0.428	0.714
B2 microglobulin	1	0.666	0.9	1

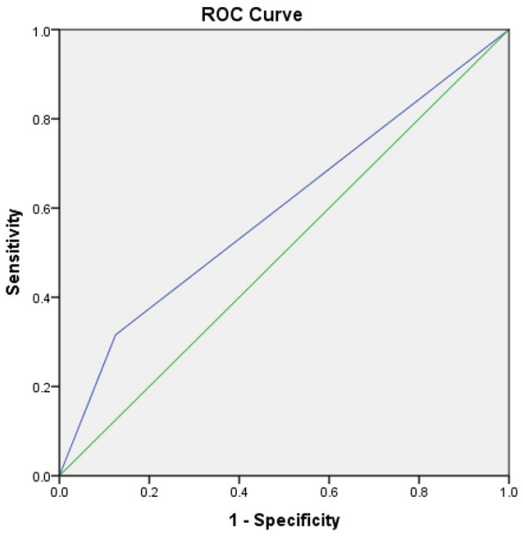

Figure 2: ROC curve of Amniotic fluid volume in predicting postnatal renal function in antenatally diagnosed LUTO : AUC 0.595 (0.406- 0.785).

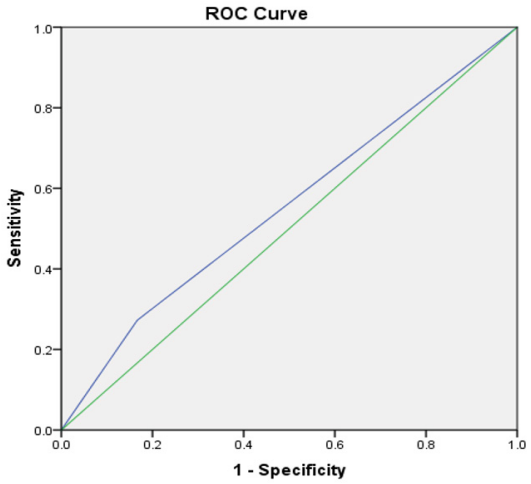

Figure 3: ROC curve of Floppy bladder in predicting postnatal renal function in antenatally diagnosed LUTO: AU0.553 (0.341-0.765).

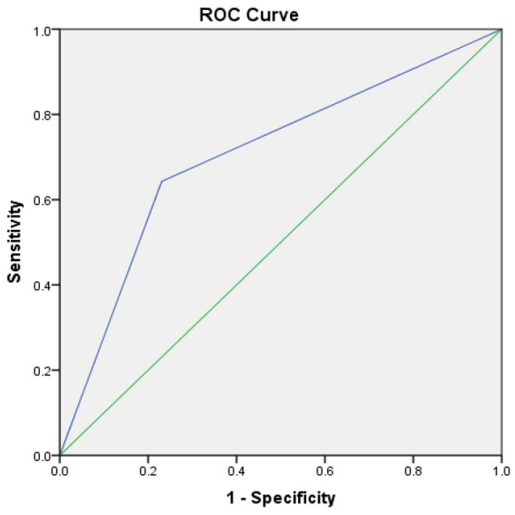

Figure 4: ROC curve of renal dysplasia in predicting postnatal renal function in antenatally diagnosed LUTO: AUC 0.706 (0.505-0.908). ROC curve for B2 microglobulin could not be produced due to small sample size.

Discussion

There are limited studies which have tried to describe predictive markers to assess the postnatal outcome in cases of LUTO. In a meta-analysis by Morris et al. [6], the ultrasound parameter with the best predictive value of postnatal renal function in survivors was renal cortical appearance with a sensitivity of 57% and specificity of 84%. In a study by Duin et al (3), a prediction model using renal hyperechogenicity and abnormal amniotic fluid volume at initial diagnosis had fair accuracy (AUC 0.699) in distinguishing adverse renal outcome (defined as eGFR <60ml/min/1.73 m2 at a mean age of 11 months). In our study the predictive accuracy of poor postnatal renal outcome based on abnormal renal cortical

Mukherjee B, et al., J Pediatr Perinatol Child Health 2024
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appearance alone is similar (sensitivity of 64.3%% with specificity of 76.9%). However, in contrast to other studies AFI shows poor predictive accuracy in our study (sensitivity 31.6% with specificity of 87.5%). This is in accordance with ERKNET consensus, where it has been stated that normal amniotic fluid volume is not a surrogate marker for good renal function.

According to study by Shannon et al. [7] an analysis of 24 LUTO cases depicted infant survival rate at 6 months 60% for rounded bladders and 0% for floppy bladders. Our study provides contrasting results where floppy bladder appears to be a poor predictor of postnatal renal function (sensitivity 27.2% with specificity of 83.3%). The contrast in results might be due to difference in outcome measures (survival at 6 months of life taken in study by Shannon et al. versus survival and renal function at 2 years of age in our study).

Muller et al. in 1993 [8] suggested that fetal urinary B2 microglobulin has good accuracy (sensitivity 83% and specificity 80%) in predicting kidney function at 2 years of age. A rise in urinary B2 microglobulin correlates with a decrease in glomeruli, corresponding to the severity of renal damage [9]. In a survey by Dreux et al. [5], fetal urine β2-microglobulin was found to be the best single marker for the prediction of long-term renal function at 10 years of survival, with 87% sensitivity and 72% specificity for a 5.0 mg/L cut-off value. Three serial measurements of fetal serum B2 microglobulin have been proposed instead of a single sampling, as the measurement of the last sample improves the accuracy (sensitivity 96.4% vs 64.3%, with similar specificity), as stated by Spaggiari et al. [10]. In our study, B2 microglobulin (on the last sample of three serial vesicocentesis) had good predictive value of poor postnatal renal function (sensitivity of 100% with specificity of 90%), which is comparable to previous studies.

Nassr et al. [11] studied that there was no correlation between the ultrasound parameters and fetal urinary biochemistry in LUTO. ERKNET consensus has proposed a combination of these parameters for predicting the severity and grading the stage of LUTO for deciding prenatal management, for which they have advocated clinical validation [4].

To the best of our knowledge, our study is the first one to compare the predictive accuracy of postnatal renal function in LUTO by comparing the ultrasound features and fetal urinary B2 microglobulin in cases with or without upper renal tract involvement. We found that the accuracy of predicting postnatal renal function is improved by assessment of fetal urinary B2 microglobulin. Here we want to highlight the fact that inspite of no upper renal tract involvement, postnatal renal function can be poor, and this is reliably picked up by high B2 microglobulin levels. The prenatal counselling and deciding the line of prenatal management would radically change in such cases. We thereby advocate the inclusion of fetal urinary B2 microglobulin analysis along with ultrasound in all cases diagnosed antenatally as LUTO for predicting the postnatal severity of the condition.

The major limitation of our study is the small number of cases as ours was a single centre study. We propose a multicentric study on a larger scale to validate these results further. The strength of our study includes data collection over a long period of time.

Conclusion

Postnatal prediction of severity of antenatally diagnosed LUTO is challenging. Assessment of fetal urinary B2 microglobulin along with ultrasound features gives us a better idea about prediction of postnatal outcome. Prenatal counselling may change based on fetal B2 microglobulin analysis, and hence should be incorporated in all cases of LUTO in clinical practice.

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Mukherjee B, et al., J Pediatr Perinatol Child Health 2024
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