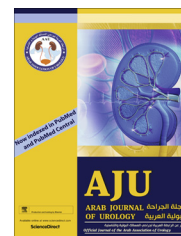




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# Posterior urethral valves: Impact of low birth weight and preterm delivery on the final renal outcome



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## KEYWORDS

Chronic kidney disease;  
Low birth weight;  
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Posterior urethral valves;  
Prognosis

## ABBREVIATIONS

(L)(N)BW, (low) (normal) birth weight;  
CKD, chronic kidney disease;  
NICU, Neonatal Intensive Care Unit;  
PUVs, posterior urethral valves;  
US, ultrasonography;

**Abstract Objective:** To investigate the relationship between low birth weight (LBW; <2.5 kg) and preterm delivery (<37 weeks gestational age) and final renal outcome in infants with posterior urethral valves (PUVs), emphasising the risk factors for the development of chronic kidney disease (CKD).

**Patients and methods:** A retrospective review was performed for all infants with PUVs who were treated between 1990 and 2010. In all, 52 infants were identified to have LBW and/or delivered preterm (Group 1). Infants in Group 1 were compared with a matching group (Group 2) of 60 full-term normal birth weight (NBW) infants with PUVs managed during the same period. The outcome of both groups was analysed.

**Results:** During follow-up, CKD developed in 17 (32.5%) and 22 patients (36.5%) in Groups 1 and 2, respectively ( $P = 0.812$ ). Patients with LBW or delivered preterm had significantly higher incidence of oligohydramnios ( $P = 0.009$ ), increased risk of vesicostomy ( $P < 0.001$ ), longer hospital stay ( $P < 0.001$ ), and higher incidence of vesico-ureteric reflux (VUR,  $P = 0.024$ ). In the LBW patients, initial serum creatinine, nadir serum creatinine, oligohydramnios and Neonatal Intensive Care Unit (NICU) length of stay were significant predictors of final renal outcome ( $P < 0.001$ ,  $P = 0.002$ ,  $P = 0.004$  and  $P = 0.012$ , respectively).

**Conclusion:** In our cohort of LBW and preterm delivery infants with PUVs, outcomes were similar to those of NBW full-term infants with PUVs but with an

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VCUG, voiding  
cystourethrography

increased risk of vesicostomy, longer hospital stay, and higher incidence of VUR. LBW was associated with oligohydramnios, longer NICU admission, high initial and nadir serum creatinine, which were associated with a poor prognosis.

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## Introduction

Posterior urethral valves (PUVs) are the most common cause of congenital lower urinary tract obstruction in male infants, leading to varying degrees of renal and bladder dysfunctions [1–5]. Due to advances in antenatal screening, almost all cases are now detected antenatally [5,6]. During pregnancy, foetal problems can occur due to PUVs, such as oligohydramnios, pulmonary hypoplasia, renal dysplasia, intrauterine growth retardation, and preterm delivery. If early prenatal detection of PUVs is documented, some centres offer termination of pregnancy, especially if the kidneys are severely affected; however, this is not the common scenario [5,6].

Foetal intervention was introduced to alleviate urethral obstruction prenatally aiming to prevent postnatal renal and bladder damage; however, the results have been frustrating [7,8]. Lung immaturity is a major problem in low birth weight (LBW) infants with PUVs and associated oligohydramnios, which usually require prolonged mechanical ventilation and admission to the Neonatal Intensive Care Unit (NICU). Over the last two decades there have been significant improvements in the medical care for preterm and LBW infants that have led to a decrease in the mortality rate.

Preterm delivery for patients with PUVs is not uncommon and dealing with this subset of patients is quite challenging [9]. Initial vesicostomy is the preferred mode of management in preterm or LBW infants due to the unavailability of appropriate instruments and/or a small calibre urethra. However, with the advent of neonatal scopes, neonatal PUV ablation can be done for these infants at an early age.

The purpose of the present study was to determine the incidence of chronic kidney disease (CKD) and the factors that can determine this outcome in infants who underwent PUV management and were confirmed to have a preterm delivery or LBW. The hypothesis was that LBW and preterm infants may have postnatal impaired nephrogenesis that could predispose to renal dysfunction later in life and adding a major pathology such as PUVs may result in worse renal outcomes.

## Patients and methods

Between 1990 and 2010, 315 infants with PUVs were diagnosed and treated at two tertiary centres. After obtaining Institutional Review Board approval, a retro-

spective review was performed of all infants who were diagnosed with PUVs born with a birth weight (BW) of <2.5 kg or at <37 weeks of gestation (Group 1). Another group of infants were treated during the same period of the study who were full term and had a normal BW (NBW) and comprised the control group for comparison (Group 2). The outcome of both groups was analysed with the focus on antenatal ultrasonography (US) results, BW, gestational age, associated oligohydramnios, associated respiratory distress, admission to the NICU, age and mode of management, postoperative complications, and long-term renal outcome.

In Group 1 patients, induction of delivery was necessary in 23 (44%) due to either oligohydramnios with bilateral significant hydronephrosis or intrauterine growth retardation. In all, 20 patients were born by Caesarean section and 32 were born vaginally. All patients in Group 1 were admitted into the NICU for varying periods for respiratory support, fluid and electrolyte balance, and nutrition. Bladder decompression by transurethral or suprapubic catheters was necessary in all the patients until surgical intervention. Serum electrolytes, blood urea nitrogen and creatinine levels were measured as markers for renal function in all patients at presentation and at time of PUV ablation. Renal US and voiding cystourethrography (VCUG) were carried out in all patients to confirm the diagnosis and as a baseline for future follow-up.

Surgical intervention was primary PUV ablation in most of the patients (82%), while cutaneous vesicostomy was indicated in those for whom PUV ablation could not be performed due to a small calibre urethra or unavailability of suitable instruments. The mean age at surgery was 26 and 22 days for Groups 1 and 2, respectively. PUV ablation was done, regardless of the infant's weight, according to the urethral calibre using 7.5, 8.5 or 10 F cystoscopes with a cold knife to avulse the PUV leaflets at the 5, 7, and 12 o'clock positions. Vesicostomy was performed using the Blocksom technique in 18 of the 52 patients in Group 1 and in two of 60 patients in Group 2. All procedures were done under general anaesthesia.

The patients were followed-up every 3–6 months and were evaluated clinically by physical examination and blood pressure measurement and radiologically by renal and bladder US. A VCUG was ordered once to ensure adequate PUV ablation and repeated if necessary. In addition, urine analysis, urine culture and serum crea-

tinine measurements were performed. Initial serum creatinine was obtained 48 h after delivery and nadir serum creatinine was the lowest level of creatinine obtained during follow-up irrespective of age. The GFR was calculated using Schwartz formula [10] and corrected for gestational age, while CKD was defined by the National Kidney Foundation guidelines [11]. The USA National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification divides CKD into five stages according to the extent of a patient's loss of renal function. A GFR of  $\geq 90$  mL/min/1.73 m<sup>2</sup> is considered normal unless there is other evidence of kidney disease. Stage 4 is defined by a GFR of 15–29 mL/min/1.73 m<sup>2</sup>, and stage 5 by a GFR of  $< 15$  mL/min/1.73 m<sup>2</sup>.

Patients who were followed-up for  $\geq 2$  years were included in the study. Exclusions included: eight patients who died from urological and non-urological causes, 12 patients with associated congenital anomalies; three who underwent antenatal intervention; 11 patients who underwent high urinary diversion (five in Group 1 and six in Group 2); nine patients with incomplete charts, and seven patients who missed follow-up.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®, version 14, SPSS Inc., Chicago, IL, USA). We used binary and logistic regression analysis. Values are given as mean (SD), unless otherwise stated. The Student's *t*-test was used for comparison of means, while the chi-square test was used to compare numbers and percentages. Incidence of CKD was computed using the Kaplan–Meier estimate and compared using the log-rank test. All tests were two-sided. Multivariate analysis was performed using Cox proportional hazards. A  $P < 0.05$  was considered statistically significant.

## Results

Group 1 included 52 patients with a mean (range) BW of 1.95 (0.940–2.650) kg and a mean (range) term of 33 (28–36) weeks. While Group 2 comprised 60 consecutive full-term patients with NBW (mean 3.200 kg). The mean (median; range) follow-up was 5.2 (4.3; 2–14) years in Group 1 and 5.5 (6.5; 2–20) years in Group 2. CKD developed at the end of follow-up in 17 patients (32.5%) in Group 1 and 22 (36.5%) in Group 2, respectively ( $P = 0.812$ ). Comparisons between the two groups are shown in Table 1.

### Univariate and multivariate analysis for Group 1 patients

Initial serum creatinine and nadir serum creatinine levels were significant predictors of final renal outcome ( $P < 0.001$  and  $P = 0.002$ , respectively). In addition, associated oligohydramnios and NICU length of stay were statistically significant predictors for CKD in those patients ( $P = 0.004$  and  $P = 0.012$ , respectively; Fig. 1).

However, BW and term and associated respiratory distress were not statistically significant factors. Furthermore, age at intervention and mode of intervention (PUV ablation vs vesicostomy) had no significant effect on the final renal outcome (Table 2).

Multivariate analysis showed that both initial serum creatinine and nadir serum creatinine levels remained significant positive predictors of CKD ( $P < 0.001$  and  $P = 0.02$ , respectively). Whereas, oligohydramnios and NICU length of stay were not ( $P < 0.94$  and  $P = 0.07$ , respectively; Table 3).

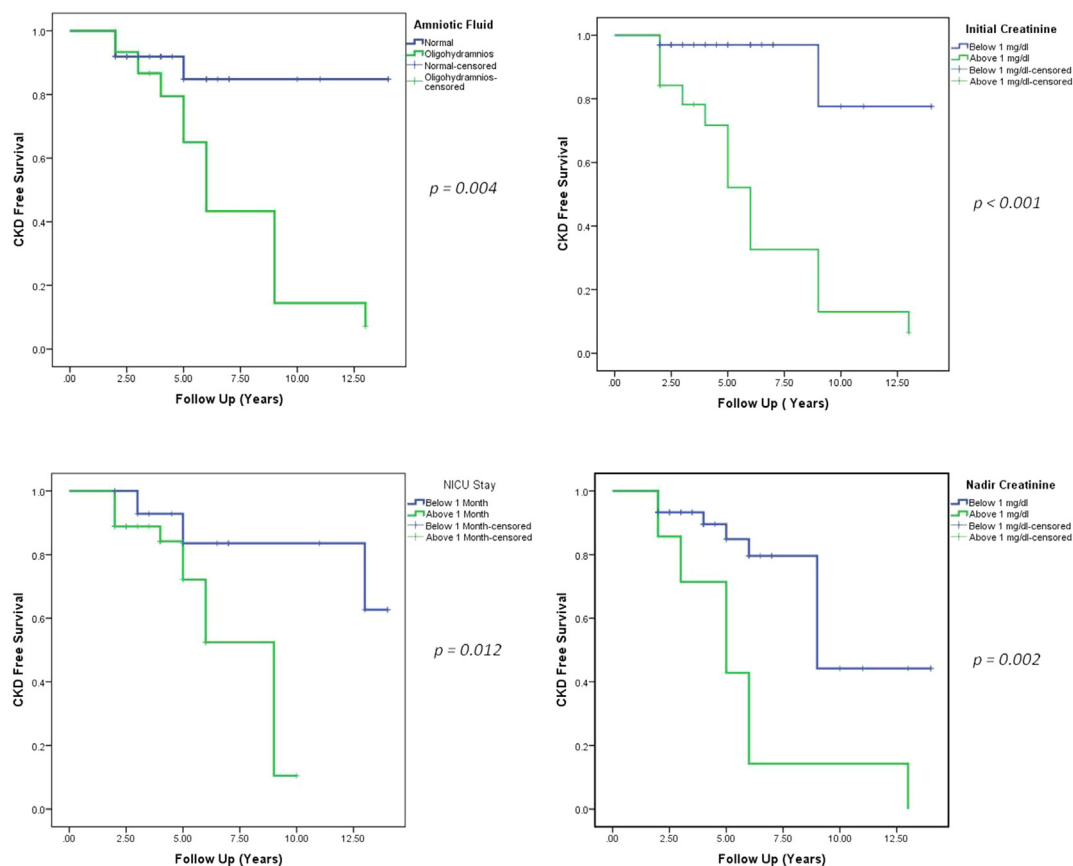
## Discussion

PUVs account for  $\sim 10\%$  of all prenatally diagnosed urinary obstructions and can produce unfavourable

**Table 1** Characteristics of infants in Groups 1 and 2.

Variable	Group 1 Preterm/LBW	Group 2 Full-term/NBW	<i>P</i>
Number of patients	52	60	
Birth weight, g, mean	1.950	3.200	$< 0.001^*$
Gestational age, weeks, mean	33	38	0.397
Oligohydramnios, <i>n</i> (%)	15 (29)	5 (8)	0.009*
Age at intervention, days, mean	26	22	0.692
Initial management, <i>n</i> (%)			$< 0.001^*$
Primary PUV ablation	34 (65)	58 (97)	
Vesicostomy	18 (35)	2 (3)	
Hospital stay, days, mean	44	6	$< 0.001^*$
Creatinine level, mg/dL, mean			
Initial	1.42	1.38	0.132
Nadir	0.79	0.76	0.416
Final	1.22	1.31	0.096
Presence of VUR, <i>n</i> (%)	37 (71)	29 (48)	0.024*
Follow-up period, years, mean	5.2	5.5	0.185
Incidence of CKD, <i>n</i> (%)	17 (32.5)	22 (36.5)	0.812

\* Statistically significant.



**Figure 1** Kaplan–Meier curve showing incidence of CKD stratified by: (A) amniotic fluid volume; (B) serum creatinine at presentation; (C) NICU admission period; and (D) nadir creatinine.

long-term renal and bladder sequelae [12–14]. When infravesical obstruction is severe, it can be lethal either *in utero* or during the perinatal period [14]. In recent decades, survival of patients with PUVs has improved significantly; however, morbidity remains high despite improvements in prenatal detection and intervention. There are no previous reports that ascertain the effect of LBW and preterm delivery on the final renal outcome in patients with PUVs. Thus, the present study was conducted to investigate outcomes in LBW and preterm infants with PUVs, focusing on several risk factors for progression to CKD.

Primary PUV ablation is the mainstay of treatment but in this patient subgroup it presents particular difficulty due to the tiny calibre of the urethra, which presents a challenge for even the smallest commercially available paediatric cystoscopes [4,9,12]. In this scenario, a cutaneous vesicostomy is a valid alternative mode of management with comparable outcomes. Previous studies have reported that urinary diversion in patients with PUVs is comparable to PUV ablation in terms of resultant renal and bladder functioning [4,12,14]. The present study is concordant with these studies, as there was no difference between the two types of management as regard final renal outcome. Most of our vesicostomy

cases were done during the early period of the study before the introduction of the new small calibre scopes; however, when we evaluated the follow-up period between the two groups (vesicostomy vs PUV ablation), as it could have been a source of results bias, we did not find the difference to be statistically significant.

In the present study, the mortality cases were excluded from the cohort because the exact cause of death in these cases was compound between respiratory, renal and cardiac failure. For religious reasons, termination of pregnancy is prohibited in our communities and thus we cannot compare mortality rates between these cases and others reported from previous studies that had cases of termination.

The published incidence of CKD in patients with PUVs varies widely, ranging from 13% to 45%, and the incidence increases with the duration of follow-up [1,5,13–16]. In the present study, the incidence of CKD, after a mean follow-up of 5 years, was similar in Group 1 and 2 patients (32.5% vs 36.5%) and comparable to most published studies [13–16]. This means that LBW and preterm delivery are not associated with worse renal outcomes, as we had expected, and the prognosis does not differ from those with a NBW and full-term gestation. Although the present cohort of patients

**Table 2** Univariate analysis of tested variables in Group 1.

Variable	Total, <i>n</i>	Normal renal function, <i>n</i>	CKD, <i>n</i>	<i>P</i>
Number of patients	52	35	17	
Amniotic fluid volume				
Normal	37	33	4	0.004*
Oligohydramnios	15	2	13	
Birth weight, kg				
< 2	21	13	8	0.670
> 2	31	22	9	
Birth term, weeks				
< 33	28	19	9	0.071
> 33	24	16	8	
Respiratory distress				
Yes	33	20	13	0.507
No	19	15	4	
NICU stay, month				
< 1	16	13	3	0.012*
> 1	36	22	14	
Initial serum creatinine, mg/dL				
< 1	33	31	2	< 0.001*
> 1	19	4	15	
Nadir creatinine, mg/dL				
< 1	43	33	10	0.002*
> 1	9	2	7	
Initial management				
Primary PUV ablation	34	25	9	0.067
Vesicostomy	18	10	8	

\* Statistically significant.

**Table 3** Multivariate regression analysis of factors affecting CKD-free survival in Group 1.

Dependent variable	Co-efficient		<i>t</i>	<i>P</i>
	<i>B</i> (95% CI)	SE		
Oligohydramnios	0.01 (-0.31 to 0.34)	0.16	0.08	0.94
Initial creatinine	0.70 (0.48–0.93)	0.11	6.37	< 0.001*
Nadir creatinine	0.33 (0.05–0.60)	0.13	2.42	0.02*
Hospital stay	0.17 (-0.02 to 0.35)	0.09	1.85	0.07

\* Statistically significant.

may be subject to selection bias, so this would be a valid investigation for future prospective studies.

It has been suggested that there is an association between BW, renal size and number of nephrons [17,18]. As nephrogenesis continues until 36 weeks of gestation, preterm neonates at < 33 weeks are liable to be nephron deficit at birth [17,18]. In addition, preterm delivery is also associated with limited postnatal renal growth until the age of 2 years [18,19]. In the present study, there was no difference in the renal outcome of patients who were born either before or after 33 weeks of gestation or below or above 2 kg BW. The lack of a statistically significant difference may be due to the size of the study group. However, gestational age at diagnosis is more important than term of delivery for predicting final renal outcome [6,20].

A normal volume of amniotic fluid, which is mainly produced by the kidneys, is of vital importance for lung growth and skeletal development [8,21,22]. Severe oligohydramnios or anhydramnios, secondary to diminished foetal urine output, leads to a small uterine cavity and hence interferes with normal foetal growth and expansion. Several studies have shown the prognostic effect of oligohydramnios on final renal outcome in which poor renal outcome was detected in > 80% of patients [6,23,24]. Our early report in 2008 showed an incidence of CKD of 55% for prenatally diagnosed cases of PUVs with associated oligohydramnios; however, cases of pregnancy termination were not included [6]. In the present study, the incidence was as high as 86% in LBW and preterm patients. This confirms the high prognostic value of amniotic fluid volume on final renal outcome.



Nadir serum creatinine after PUV management is a well-known prognostic factor for long-term renal outcome [13,25–28]. Different nadir creatinine threshold levels have been postulated to predict renal outcome, generally 0.8 and 1 mg/dL. In the present study, the threshold level of 1 mg/dL was used based on our previous work [13,27]. When nadir creatinine was < 1 mg/dL, the risk of developing CKD was significantly lower. This finding concurs with previous studies in which a high nadir creatinine level was associated with worse long-term renal outcomes [12,25–27].

Furthermore, initial or presenting serum creatinine has also been correlated with the final renal outcome [13,27–30]. The present study data similarly showed an association between high creatinine at presentation and risk of CKD. Actually, the initial creatinine of most patients was measured after a varying period of bladder drainage before PUV ablation or vesicostomy according to the general condition of the patient. The study of Denes et al. [30] in 1997 established that serum creatinine levels after initial bladder drainage had a clear prognostic correlation with final renal outcome.

The present study has some limitations being retrospective and including relatively few patients. Patients with inadequate charts and who were lost to follow up were excluded from the study, which may be a source of bias. Also patients who underwent high diversion were excluded because they represented a different mode of treatment that did not prove to be more efficient compared to PUV ablation, although they were nearly equally distributed in both groups.

## Conclusions

In the present study, LBW and preterm delivery did not carry a significant additional risk for patients with PUVs as regard the final renal outcome. There is an increased incidence of oligohydramnios, rate of vesicostomy, and longer hospital stay among such patients. Associated oligohydramnios, longer NICU admission, high initial and nadir serum creatinine carry a poor prognosis for LBW patients. On multivariate analysis, initial serum creatinine and nadir serum creatinine remained significant predictors of CKD. These findings are important in the counselling of the patients' families.

## Ethical Standards

Ethical standards were followed and a review board approval was obtained.

## Conflict of Interest

There is no conflict of interest.

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