

# Renal outcome among children with posterior urethral valve: When to worry?

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## Abstract

**Introduction:** Posterior urethral valve (PUV) is a congenital obstructive defect of male urethra that is diagnosed early during antenatal period with a presence of hydroureteronephrosis and associated with several morbidities including chronic kidney disease (CKD) that requires management, therefore, this study aim to evaluate the renal outcome of endoscopic valve ablation and urinary tract diversion in children with PUV, “when to worry, and what to do.”

**Methodology:** This is a retrospective cohort study reviewing medical records of all patients diagnosed with PUV that has been managed in Pediatric Urology Unit at King Abdul-Aziz Medical City, Jeddah in the period of 1998–2008 with proven diagnosis at age younger than 16 accounted for 39 patients, and with different multiple demographics such as antenatal and postnatal ultrasound findings, serum levels of preoperative creatinine, mode of surgical treatment (i.e., endoscopic valve ablation and urinary diversions). Patients were divided into two groups according to the initial surgical intervention. Patient’s characteristics and other variables were analyzed; *t*-test and Chi-square test were used.

**Results:** During the follow-up period, (45%) developed CKD with a mean time of 5.5 years, 18% reach to end stage renal disease (ESRD), (10%) requiring dialysis. Abnormal creatinine level was detected in 69% (27/39) of our patients before the intervention and normalized in 97% after intervention. In comparison between the two intervention groups, CKD were developed in 60% of patients with urinary diversion in comparison to 33% for the endoscopic ablation group with no statistical significance with  $P = 0.09$ . The time to develop CKD was faster in the diversion group with mean age of 18 months (standard deviation [SD] 2 years) in comparison to endoscopic ablation group with mean age 6 years (SD 4 years). Similar results were observed for development of ESRD, patients who underwent diversion had slightly higher incidence of ESRD. In our cohort group, the main determinant for deterioration of the future kidney function was the level of serum creatinine, preoperatively. Moreover, recurrent urinary tract infections (UTIs) were developed in 64% of our cohort group and 49% of our population diagnosed with voiding dysfunction at 6 years of age.

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**Conclusion:** A child with PUV who has a risk factor does have an increased potential of developing CKD, knowing that the type of intervention offered to treat PUV has no impact on the outcome. Furthermore, not having any of the study mentioned risk factors doesn't rule out the possibility of developing comorbidities which suggest that any child with PUV always need to be worried about and longer follow-up is indicated. Early intervention, check cystoscopy after ablation, close follow-up with appropriate laboratory and radiological investigation when necessary are recommended, and to improve the quality of data to the level reaching to a meaningful conclusion with high accuracy, a national database system from all centers across the country should be implemented.

**Keywords:** Children, chronic kidney disease, posterior urethral valve, recurrent urinary tract infection, urinary diversion, valve ablation, voiding dysfunction

## INTRODUCTION

Posterior urethral valve (PUV) is a congenital obstructive defect of the male urethra and one of the most common causes that lead to lower urinary tract obstruction in male neonates. The incidence rate is estimated to occur in 1 in 8000 in United States while in Europe is 1 in 25,000 male live births.<sup>[1,2]</sup> However, the incidence in our setting (i.e., Saudi Arabia) is still unknown.

Most patients diagnosed early during antenatal is due to the presence of hydronephrosis on prenatal ultrasound and subsequently confirmed through voiding cystourethrography (VCUG) during the postnatal period, however, some patients presented late in their age.<sup>[3]</sup>

PUV is associated with several morbidities and the pathology has detrimental effects associated with characteristic changes of the bladder, kidney and entire urinary system. This includes bladder diverticula, hydronephrosis, urinary tract infection (UTI), urinary incontinence (UI), sepsis, chronic kidney disease (CKD) to end stage renal disease (ESRD) and even death.<sup>[4-6]</sup>

In children with PUV, there is increasing concern over the utility of surgical intervention in preserving their kidney function and to prevent recurrence of symptoms that could lead to several consequences, especially for follow-up cases after the surgical management. Despite the improvement in the technique for endoscopic valve ablation, urinary diversion (vesicostomy, ureterostomy, or pyelostomy) is still considered a valid postnatal management of PUV. However, many questioned the efficacy of urinary diversion in improving the renal outcome in comparison to endoscopic intervention, as the deterioration of renal function will occur regardless to the intervention selected as a consequence of congenital renal dysplasia which coincide with PUV. Moreover, defunctionalizing the bladder as the result of the diversion was not fairly popular.

Therefore, this study aimed to evaluate the renal outcome of endoscopic valve ablation and urinary tract diversion in children with PUV.

## METHODOLOGY

This was a retrospective cohort study by reviewing medical records of all patients diagnosed with PUV that has been managed in Pediatric Urology Unit at King Abdulaziz Medical City, Jeddah in the period of 1998–2008. Patients at the age of <16 years with proven diagnosis established by VCUG were all included in this study.

### Inclusion criteria

Patients' diagnosed with PUV by VCUG preoperatively and documented through cystoscopy later, surgery performed in our center within 1<sup>st</sup> month of age, usually, and completed serial creatinine measurement over 2 years' follow-up period. We excluded patients who died before intervention.

Patient demographics, antenatal and postnatal ultrasound findings, VCUG, follow-up, urinalysis, serum levels of creatinine, glomerular filtration rate (GFR), mode of surgical treatment (i.e., endoscopic valve ablation and urinary diversions) and postsurgical complications were assessed.

Based on the ultrasound findings, the Society of Fetal Urology (SFU) grading system,<sup>[7]</sup> was used to grade the severity of hydronephrosis that classified as grade I; mild splitting of the pelvis; Grade II, evident splitting and dilation of the renal pelvis; Grade III, dilated pelvis and calices; and Grade IV, dilated pelvis and calices and parenchymal thinning. In addition, International Reflux Grading System was also used to grade the vesicoureteric reflux (VUR).<sup>[8]</sup>

Renal function was evaluated by albumin excretion and GFR estimated from concentration of serum creatinine

in relation to mode of treatment. Albuminuria or albumin excretion of more than 30 mg/day and GFR <60 ml/min/1.73 m<sup>2</sup> is the basis to rule out patient for CKD. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative<sup>[9,10]</sup> classified CKD into stages; Stage 1, persistent albuminuria with an estimated GFR higher than 90 mL/min/1.73 m<sup>2</sup>; Stage 2, persistent albuminuria with a mild reduction in GFR of 60–89 mL/min/1.73 m<sup>2</sup>; Stage 3, a moderate reduction in GFR of 30–59 mL/min/1.73 m<sup>2</sup>. Stage 4, a GFR of 15–29 mL/min/1.73 m<sup>2</sup> and Stage 5, describe as ESRD with a GFR <15 mL/min/1.73 m<sup>2</sup> were children required dialysis. Voiding dysfunction and recurrent UTI and other complications developed were also assessed.

Patients were divided into two groups according to the initial surgical intervention which was performed. Group one where offered endoscopic valve ablation only and Group two were offered urinary diversions with or without valve ablation. All interventions were performed by single surgeon, and the selection of cases to each group was according to his decision. The selection of the intervention was the surgeon recommendation but patients’ family decision. The surgeon recommendations depended on the improvement of creatinine following the catheter drainage just before surgery; adequacy of the urethra to accommodate the scope, and the presence of severely dilated ureter but no evidence of reflux on VCUG.

Patients characteristics and other variables were analyzed and presented through frequency, percentages, mean, standard deviation (SD) and interquartile range (IQR). To test for differences, Student’s *t*-test was used for continuous variables between the two groups while Chi-square test for categorical or ordinal variables. All statistical tests were two-sided, and a *P* < 0.05 was considered statistically significant. Analyses were performed by use of the SPSS statistical package (IBM Corp., Released 2012, IBM SPSS Statistics for Windows, version 21.0. Armonk, NY, USA: IBM Corp.).

This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center, Jeddah, Saudi Arabia. The need for informed consent was waived due to the retrospective nature of the study.

**RESULTS**

**Patient’s characteristics**

During the study period, we included 39 children with PUV that was managed by the same surgeon in our setting and their records were fulfilling the inclusion and exclusion

criteria. Most of our study population were delivered through spontaneous vaginal delivery (18/39, 72%), and 9 neonates (23%) are premature (<37 weeks of gestation). The median weight at delivery was 2.8 kg (IQR = 1.16 kg). The median follow-up period was 9 years (IQR = 14). Coincidental anomalies, apart from VUR disease, were documented in 12 neonates (31%) and it is listed in Table 1. Oligohydramnios was present antenatally in 21 patients (55%) and only 4 neonates (10%) were diagnosed with lung hypoplasia, postnatally. Antenatal hydronephrosis were detected in 30 patients (77%) and 23% were missed, i.e., considered normal kidneys on antenatal follow-ups.

**Postnatal evaluation**

The initial ultrasound was performed in median age of 2 days old newborn. Right kidney hydronephrosis was detected in 92% of the patients with median anterior-posterior (AP) diameter 14 mm (IQR = 17 mm), and 48% of them had Grade 4 in SFU grading system of severity. Also left kidney hydronephrosis was detected in (92%) with median AP diameter 6 mm (IQR = 13.4) and 45% of them had Grade 4 SFU, Table 2. VCUG was performed at median age of 4 days and detected 92% PUV, Table 3. VUR was documented in 65% of cases and 80% of them were high grade reflux.

**Intervention groups**

Patients were divided according to type of intervention into two groups. Group one, 24 patients (61%), underwent endoscopic ablation of the valve only, and Group two, 15 patients (39%), had urinary diversion, (either vesicostomy 56% or ureterostomy 44%) with or without valve ablation.

**Renal outcome**

Abnormal creatinine level was detected in 69% (27/39) of our patients before the intervention and normalized in 97% (38/39) post the intervention with the median value pre/post-intervention was 73 and 56, respectively. During the follow-up period, 17 patients (45%) developed CKD with a mean time of 5.5 years (SD 3 years), 7 patients (18%)

**Table 1: Types of associated congenital anomalies in the study population**

Types of associated anomalies with PUV	Frequency
Undescended testes	5
Lung hypoplasia	4
CNS malformations	3
Multicystic dysplastic kidneys	2
Myelomeningocele	1
Ectopic kidney	1
Renal agenesis	1
Duplicate bladder	1
Polycystic kidney disease	1

PUV: Posterior urethral valve, CNS: Central nervous system

reach to ESRD, and four patients (10%) requiring dialysis. Figure 1 shows the serial creatinine levels over time in the study population. The incidence of hypertension in our study population was 8%, median age at development was 7 years.

In comparison between the two interventions, CKD were developed in 60% of patients with urinary diversion in comparison to 33% for the endoscopic ablation group, this difference was not statistically significant with  $P = 0.09$ , and odds ratio (OR) = 3, (95% confidence interval [CI]: 0.8–11.4). The time to develop CKD was faster in the diversion group with mean age of 18 months (SD 2 years) in comparison to endoscopic ablation group with mean

age 6 years (SD 4 years). Similar results were observed for development of ESRD, patients who underwent diversion had slightly higher incidence of ESRD, OR = 2.55, (95% CI: 0.48–13.46), and it was not statistically significant.

In our cohort group, the main determinant for deterioration of the future kidney function was the level of serum creatinine, preoperatively. Neonates with abnormal creatinine level before intervention had a significantly higher risk in developing CKD, than patients with normal creatinine before intervention; OR = 5.6 (95% CI: 1.02–31.09;  $P = 0.039$ ).

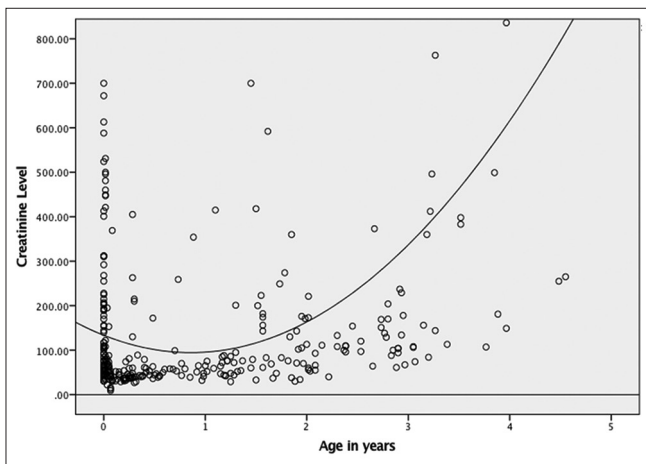
**Other outcomes**

Overall, recurrent UTIs were developed in 64% of our cohort group and 49% of our population diagnosed with voiding dysfunction at 6 years of age. In a multivariate analysis module, there were no association detected between the development of voiding dysfunction or recurrent UTIs with the type of intervention offered to patients, and the relationship was statistically insignificant with a  $P = 0.3$  and  $0.5$ , respectively.

**DISCUSSION**

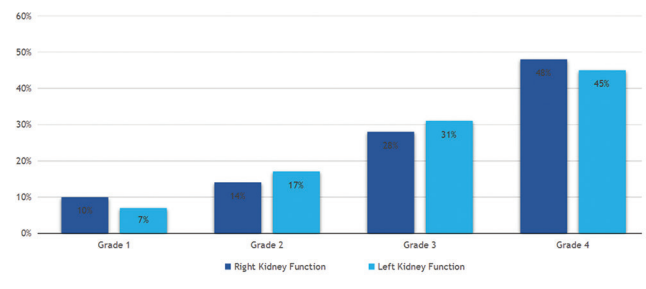
PUV is the most common cause of congenital infravesicle obstruction in male neonates, with incidence ranges from 1 in 3000 to 1 in 8000.<sup>[11,12]</sup> This disease shares the irony of a relative simple diagnosis but a significant long term consequence. The presentation is often antenatal and imaging that shows pathognomic findings confirm the diagnosis postnatal. Based on postmortem dissection in 1769 by Morgagni, and with results confirmed by Langenbeck in 1802 this disease was recognized and described stated as valve like leaflets.<sup>[13]</sup> The first endoscopic description and classification of PUV by Hugh Hampton Young was in 1919, since then several reports had linked PUV and renal impairment, with reported incidence of ESRD up to 40%.<sup>[14,15]</sup> Despite knowing that the presence of PUV will require immediate addressing and intervention by endoscopic ablation or urinary diversion, the insult of the disease to the urinary system will vary in the extent and will require an extended care of pediatric urologist and pediatric nephrologist.

What makes PUV a disease worth studying despite relative low incidence is the acuity of the presentation and the seriousness of the impact and comorbidities developed by the infant who has affected by the disease, such as pulmonary hypoplasia and physical stigmata of oligohydroamnions, including potter facies, clubfeet, and deformed hands, poor abdominal muscle tone. Mortality

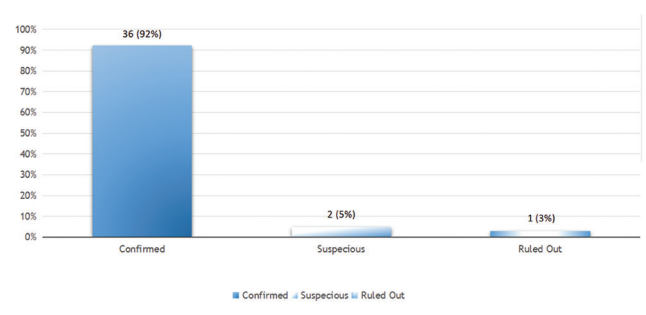


**Figure 1:** The serial creatinine levels over time in the study population

**Table 2: Society of fetal urology grading**



**Table 3: Voiding cystourethrography**





from a severe lower urinary tract obstruction is possible when pulmonary hypoplasia occurs, and it is considered the most profound complication of this pathology.<sup>[13]</sup>

Previously it was hypothesized that patients who didn't respond to initial bladder drainage, by improvement in creatinine level, should be treated with supravescicle diversion, ureterostomies, or pyelostomies.<sup>[16]</sup> This hypothesis was challenged and rejected on several occasions, and renal dysplasia was identified as the main reason for worsening of kidney function during follow-up, regardless the type of intervention was offered to patients.<sup>[14,17]</sup> Although renal impairment in PUV is proven to be due to renal dysplasia and obstructive uropathy, some debates are still ongoing regarding whether renal damage is secondary to obstruction or concurrent with congenital renal dysplasia.

An old hypothesis state that the reflux serves as a pop-off mechanism in which the dysplastic kidney with reflux act as a pressure reservoir preventing damage of the contralateral kidney which termed vesicoureteral reflux and dysplasia (VURD), but the question which need to be studied and answered in another research is, will this VURD confer a protective benefit on the long term renal prognosis, which was not suggested in several previous reports.<sup>[18]</sup>

This study confirmed the later findings and reported that 33% of our patients who had endoscopic intervention will develop some form of CKD by the age of 6 years, while for supravescicle diversion group, the rate of CKD development was 60%, by the age of 18 months. Therefore, not only the diversion group has high rate, but also those patients develop renal impairment before their second birthday. This difference was clinically important, but was not statistically significant. Remarkably, a significant improvement in serum creatinine level, early postoperatively was reported in both groups but it was proven to be temporary only for the diversion group. There are two main theories behind this renal abnormality. First, antenatal obstruction of the posterior urethra affects the entire urinary system proximal to the level of obstruction, obstructive uropathy, and leads to significant organ dysfunction, not only the kidneys, but also the bladder, where it was document that, the prevalence of voiding dysfunction in patients with PUV was as high as 40%.<sup>[15]</sup> The obstructive uropathy process is complexed, but significant tubular damage will occur and kidneys tend to lose the concentrating capacity, therefore, nephrogenic diabetes insipidus will occur adding an extra-load on the bladder, which was already exhibiting structural and functional abnormalities, adding insult to an

injury, subsequently leads to increased intravesical pressure, and further renal damage. But this is why many researchers have thought that, supravescicle diversion would help in halting this pathophysiological cascade, unfortunately it did not. Consequently, the second theory was suggested that renal dysplasia, congenitally as coincidental abnormal development of the kidneys or acquired as a result of increased pelvic pressure in a developing kidney. This irreversible renal damage is considered the main indicator for worsening of the renal function during follow-up.<sup>[14,17,19]</sup> This abnormality is caused by abnormal ureteric budding followed by abnormal induction of the mesenchyme.<sup>[20]</sup> In our study, the only significant indicator for worsening of the kidney function was the severity of the preoperative abnormality of serum creatinine level before the initial intervention. Despite the temporary improvement in the early postoperative period, patients with severe abnormality of creatinine level, preoperatively, tend to develop CKD more frequent and much faster, regardless to the type of intervention offered. This abnormality, especially the severe ones, is suggestively caused by renal dysplasia, congenital or acquired. Therefore, supravescicle diversion rarely has any positive influence on the overall renal outcome.<sup>[20]</sup>

Other studies have shown that the renal function deterioration can be caused by bladder dysfunction, recurrent UTIs or VUR. Those factors were identified as indicators for progression to ESRD, alongside other factors, as, age at intervention, creatinine level at presentation, nadir creatinine and many more.<sup>[11,21-24]</sup> Those factors were assessed in our study in a multivariate analysis module, but unfortunately, none of them were statistically significant except the preoperative creatinine level, as described above.

Selection bias was inevitable consequence of such a retrospective research design. Moreover, most of the statistical testing were insignificant in our study including the main study objective and the multivariate analysis one, due to small sample size included in the study population, despite it was clearly demonstrated that there is a difference between the two groups favoring the endoscopic group. Although this could be challenged by the idea that most of the patients who underwent diversion were actually worse in clinical presentation and disease process hence the selection for the diversion.

Finally to answer this research question “when to worry,” despite the study limitation, we have found that the severity of abnormal creatinine level preoperatively, developing voiding dysfunction and recurrent UTI have an increased potential of developing CKD during follow-up and they are considered high risk, knowing that the type of intervention

offered to treat PUV has no impact on the outcome. Furthermore, not having any of the mentioned risk factors doesn't rule out the possibility of developing comorbidities and profound complications which suggest that once we have diagnosed an infant with PUV we should always worry and longer follow-up is necessary. For more valid results with less selection bias and generalizable conclusion, we recommend creating a national database for PUV, including all centers across the country who manage such patients, updated regularly and prospectively, as it is necessary to improve the quality of data and reaching to a meaningful conclusion with high accuracy.

## CONCLUSION

Developing CKD is common in patients with PUV and worse outcome was observed in patients with urinary diversion (60%) than endoscopic valve ablation (33%). Preoperative serum creatinine level was the main determinant of future development of renal impairment, not the type of intervention offered.

Voiding dysfunction and recurrent UTI are major contributing factors for the development of CKD during follow-up. However, absence of risk factors doesn't rule out the possibility of developing comorbidities and profound complications. Longer follow-up is necessary in children with PUV.

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## Conflicts of interest

There are no conflicts of interest.

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