

# Obstructive Uropathy Secondary to Posterior Urethral Valves: Retarding the Progression to End-Stage Kidney Disease in Children

**Keywords:** Posterior urethral valves; Obstructive uropathy; Prenatal interventions; Postnatal interventions; Renal outcomes

## Abstract

Posterior urethral valve (PUV) is the most common cause of obstructive uropathy leading to chronic kidney disease (CKD) in male newborn infants. The few children that survive have poor prognosis, with over 50% progressing to end-stage kidney disease (ESKD) within ten years. This review aims to appraise the current interventions targeted at

retarding the progression of the obstructive uropathy to late stages of CKD. With the current screening strategy, the majority of interventions are performed well after irreversible damage has occurred. Therefore, reduced mortality and improved long-term morbidity outcome from PUV will likely remain unattainable until it is possible to intervene before the onset of irreversible renal damage. Although fraught with complications and variable results, several prenatal interventions have been tried; these include vesicoamniotic shunting, vesicocentesis, fetal cystoscopy, or open fetal bladder surgery. The efficacy of these procedures however remains controversial. In retrospect, data on outcome of fetal intervention for PUV indicate that it is associated with risks of fetal and maternal morbidity or mortality without proven benefit for long-term renal outcome. The initial postnatal intervention of passing a continuously draining indwelling catheter may suffice in many cases albeit with some drawbacks. Primary valve ablation however remains the gold standard for treatment of PUV, with vesicostomy reserved for selected cases such as the very ill infant or younger infants where catheter passage is impossible or very difficult. Nonetheless, urinary diversion must be considered in selected cases with clear goals and endpoints in mind. The frequency of chronic and progressive renal impairment underscores the importance of long-term evaluation for all patients with PUV. Serial measurements of renal function, periodic urinalysis, blood pressure checks, and growth monitor should be performed for such patients.

## Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) constitute, collectively, major causes of chronic kidney (CKD) disease in children [1]. These anomalies result in obstructive uropathy which eventually leads to progressive renal dysfunction or obstructive nephropathy if there is no appropriate intervention. Posterior urethral valves (PUV) are the most common cause of obstructive uropathy leading to CKD in male newborn infants [2]. Although the true incidence of PUV is not precisely known, it is estimated to occur in 1:5000 live births [3]. Despite its high prevalence, the few children that survive have poor prognosis, with over 50% progressing to end-stage kidney disease (ESKD) in 10 years [4,5]. This underscores the importance of early diagnosis, as well as implementation of



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an appropriate management paradigm [2]. Early diagnosis and intervention to reduce urostatics and stabilize the upper tract is thus critical to delay progression of renal insufficiency [6]. Prenatal diagnosis is dependent on routine screening ultrasonography while the gold standard for postnatal diagnosis is voiding cystourethrography (VCUG) [4]. However, routine prenatal ultrasonography is currently not recommended until 20 weeks of pregnancy [7]. According to the recommended guidelines, the optimal time to perform an ultrasonographic examination, in the absence of a specific indication for first trimester screening, is between 18 and 20 weeks [7]. With the current screening strategy, the majority of interventions are performed well after irreversible damage has occurred. Reduced mortality and improved long-term morbidity outcome from PUV will likely remain unattainable until it is possible to intervene before the onset of irreversible renal damage [4]. The present review aims to appraise the current interventions targeted at retarding the progression of CKD secondary to PUV.

## PUV as a Cause of Paediatric CKD: The Global Picture

In developed countries, congenital anomalies of the kidney and the urinary tract (CAKUT) contribute to majority of the cases of paediatric CKD [1]. For instance, studies in the United States [8] and Italy [9] identify CAKUT as an important causative factor. The associated obstructive uropathies are a well-acknowledged cause of paediatric CKD which may end up in ESKD [10]. Although there is dearth of epidemiologic data on childhood CKD in developing countries, several reports from a sub-Saharan African country like Nigeria indicate the prominent role of CAKUT (particularly PUV) in the etiologic spectrum [11-17]. Generally, PUV remains the most common cause of CKD due to urinary tract obstruction in children [2]. Specifically, statistics show that its prevalence in the etiology of childhood CKD may be much as 7.8% and 13.3% in some parts

of Nigeria [13,18]. Elsewhere in the United States, approximately 10% of cases with postnatal presentation of PUV progress to CKD, sometimes decades after the initial presentation [19]. Another study in Ontario, Canada noted that impaired renal function, as determined by significantly elevated serum creatinine levels, reduced GFR, or both, was found in 23% of patients with PUV; while 11% of them progressed to ESKD [20]. In the United Kingdom, obstructive uropathy (mainly PUV) accounted for 14.9% of the cases; it ranks only behind renal dysplasia and glomerular disorders in the causative list [21]. In a hospital-based study in Iran, urologic anomalies were the most common cause of CKD in children; the most common anomaly was vesico-ureteral reflux (VUR) which accounted for 24.3% of total etiologies followed by obstructive uropathies [22]. Similarly in Iraq, Middle-East [23], Jamaica in the Caribbeans [24], as well as in Paraguay, South America [25], congenital urologic malformations were responsible for the majority of childhood CKD etiologies followed by glomerulonephritis. Again, PUV constitute a significant proportion of these urologic anomalies in these studies. In Asia, a report from India also indicates that congenital urologic anomalies were the predominant cause of pediatric CKD and accounted for 47% of etiologies [26]. In Tunisia, North Africa, urologic anomalies were equally noted as one of the chief etiologies of ESKD in children: constituting about 13% [27]. Thus, a global snap-shot of the documented data shows that obstructive uropathies, especially PUV, significantly contribute to the etiology of pediatric CKD in male subjects.

### **Prenatal Management of PUV**

PUV potentially render both kidneys at risk for abnormalities in fetal renal development, as well as impaired renal function, and may be associated with oligo-hydramnios and pulmonary hypoplasia [28]. Like other causes of congenital bladder outlet obstruction, PUV may lead to a cascade of physiologic/ pathologic consequences. For instance, it may result in bladder dysfunction, ultimately leading to a secondary functional obstruction which may therefore require painstaking management in order to optimize renal outcomes. Secondary VUR is found in 25-50% of PUV cases [29]. In a subset of patients, unilateral VUR may provide a “pop-off” effect, whereby renal tissue and function on the non-refluxing side is preserved at the expense of severe dysplasia and dysfunction in the refluxing kidney [30]. Other “pop-off” mechanisms which may relieve intrarenal pressure and thus delay or prevent progression to ESKD include development of bladder diverticulae, urinary ascites and perirenal urinomas. However, several studies show that as many as 70% of patients with PUV develop CKD Stage 3-5 [31-34]. Those with ultrasonographic findings at or before 24 weeks’ gestation are significantly more likely to have a poor renal outcome than patients with PUV detected later in pregnancy after a normal second trimester scan [35]. Notable poor prognostic factors in the post-natal period include bladder dysfunction, trough serum creatinine level greater than 1.0 mg/dl [10,36], and unilateral or bilateral VUR [37]. Although fraught with complications and variable results, several prenatal interventions have been tried in PUV; these include vesicoamniotic shunting, vesicocentesis, fetal cystoscopy, or open fetal bladder surgery [28]. The efficacy of these procedures however remains controversial. In a retrospective study to evaluate the effect of antenatal vesico-amniotic shunt placement for patients with PUV who underwent fetal

surgery, one author reported that the intervention made no difference to the outcome and long-term results of patients who underwent the procedure and those who had post-natal surgical correction [38]. Furthermore, a group of researchers assessed the impact of prenatal diagnosis and evaluation on the outcome of PUV, and documented that their outcome were not significantly improved [39]. This finding is corroborated in a review which reported that improvement of patient outcome by early detection and antenatal intervention remains to be proven [40]. Some authors however suggest that the onset of ESKD may be prevented or delayed by treating factors like bladder dysfunction, VUR, polyuria and proteinuria responsible for the slow and progressive deterioration in renal function which some of the patients manifest with over a period of time [41]. In the United States, other investigators also found that fetal intervention for PUV carried a considerable risk to the fetus with fetal mortality rate of 43%: the long-term outcomes indicating that intervention may not change the prognosis of renal function [42]. In retrospect, data on outcome of fetal intervention for PUV indicate that it is associated with risks of fetal and maternal morbidity or mortality without proven benefit for long-term renal outcome, even though the objectives of vesicoamniotic shunt placement are to prevent lung hypoplasia by shunting fetal urine from the obstructed urinary system to the amniotic space, as well as to relieve obstruction and reduce injury to the developing nephron.

### **Postnatal Management of PUV**

Despite the relief on some of the effects of congenital obstruction of urine flow through surgical interventions, many of the associated developmental and pathologic changes appear irreversible [28]. In fact, many patients with congenital obstructive uropathy, including the majority of patients with PUV, do not have complete recovery of renal function following postnatal intervention [31-34]. The initial postnatal management of PUV starts by passage of continuously draining indwelling catheter. In many cases, this procedure may suffice although the drawbacks include bladder spasms which may impair renal decompression, as well as difficulty in passing the catheter into the bladder due its elevation. This may necessitate using imaging to confirm proper catheter placement in the bladder rather than in the dilated posterior urethra. Previously there were three specific surgical interventions for PUV: vesicostomy followed by valve ablation, pyelostomy (high diversion) followed by valve ablation and primary (transurethral) valve ablation alone. Currently, vesicostomy is not the first choice drainage procedure; it is indicated in the very ill infant or younger infants where catheter passage is impossible or very difficult. Ureterostomy is an alternative high-diversion surgical option indicated in current practice only when vesicostomy fails to decompress the kidneys. Pyelostomy appears outdated; thus ureterostomy, and very rarely nephrostomy, is currently the preferred option of proximal diversion. Notably, the pathophysiologic links between the valves and function of the ureterovesical junction and upper urinary tract are crucial in determining the need for upper tract surgery [43]. Sometimes, upper tract function remains abnormal and results in complications which necessitate early ureteral and upper tract surgical interventions. Although diagnostic tests are invaluable in making decisions about upper tract surgery in patients with PUV, these decisions are usually based on the classic clinical urologic complications like urinary extravasation (ascites), obstruction,

infection, VUR, and azotemia [43]. Primary valve ablation however remains the gold standard for treatment of PUV, with vesicostomy reserved for selected cases [20]. Nevertheless, in one retrospective study, the effect of bilateral high urinary (ureterostomy) diversion on renal and bladder function was evaluated [44]. In patients with PUV, temporary high (ureterostomy) diversion did not have a negative influence on bladder function. In addition, the intervention was noted to have achieved the immediate release of high intra-renal pressures and temporary improvement of renal function which may contribute to postponement of the onset of ESKD. The authors concluded that renal dysplasia dictates long-term renal outcomes in this group of patients [44]. However, another retrospective study revealed that long-term bladder function of patients with PUV treated with temporary supra-vesical diversion (cutaneous ureterostomy) is affected more adversely than those treated with valve ablation alone [45]. The authors retrospectively reviewed 2 series of patients with PUV who were treated initially with valve ablation preceded by bilateral cutaneous ureterostomies, or valve ablation alone in order to evaluate and compare bladder function behavior of each treatment group [45]. Furthermore, in yet another retrospective study, a group of researchers sought to compare the clinical and radiologic outcomes between valve ablation and urinary diversion for patients with PUV [46]. While maintaining that valve ablation remains the mainstay of treatment, prenatal and postnatal factors, such as renal dysplasia and urinary tract infection, respectively, were noted as determinants of long-term renal and radiologic outcomes rather than the PUV treatment. This observation is supported by other workers who confirmed that early valve ablation can be considered as the primary treatment in the majority of patients, without the need for pre-operative drainage or diversion [47].

## Conclusions

Several approaches to the treatment of patients with PUV exist, but the ideal strategy is debatable; as technological advancement evolves, more options for early intervention are emerging [40]. The role of early urinary diversion in the management of boys with PUV is limited. In spite of its potential to improve renal function in the short-term (which is very important in male patients with precarious renal function) and to defer renal replacement to a later stage, there is no convincing evidence to support its role as a way of improving long-term renal function. Its effect on long-term bladder function remains unsatisfactory. Primary valve ablation appears to result in better long-term outcomes, and thus remains the treatment of choice. Nonetheless, urinary diversion must be considered in selected cases with clear goals and endpoints in mind. Given the frequency of chronic and progressive renal impairment, the importance of long-term evaluation of all patients with PUV cannot be over emphasized. Serial measurements of renal function, periodic urinalysis, blood pressure checks, and growth monitor should be performed for such patients.

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