

Valve bladder syndrome in children: On the trail of the best strategies to prevent chronic kidney disease

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Abstract

Pediatric patients suffering from valve bladder syndrome (VBS) are at risk of developing chronic kidney disease (CKD) and renal failure in later life. Therefore, it is of vital importance to determine the risk factors and the best possible strategies for diagnosis and treatment in patients with VBS that would minimize the risk of developing CKD. In this review we have presented the current knowledge of CKD risk factors in patients with posterior urethral valve (PUV). We have also discussed possible recommendations for prenatal diagnostics procedures to be undertaken in patients with PUV, postnatal monitoring and therapeutic strategies that could reduce the risk of developing CKD in this population. Although in most cases there are no clear guidelines for appropriate clinical actions that can be undertaken in patients with PUV to minimize the risk of kidney failure, we have tried to present concise and accurate advice for physicians taking care of patients with PUV.

Key words: chronic kidney disease, valve bladder syndrome, bladder dysfunction, posterior urethral valve

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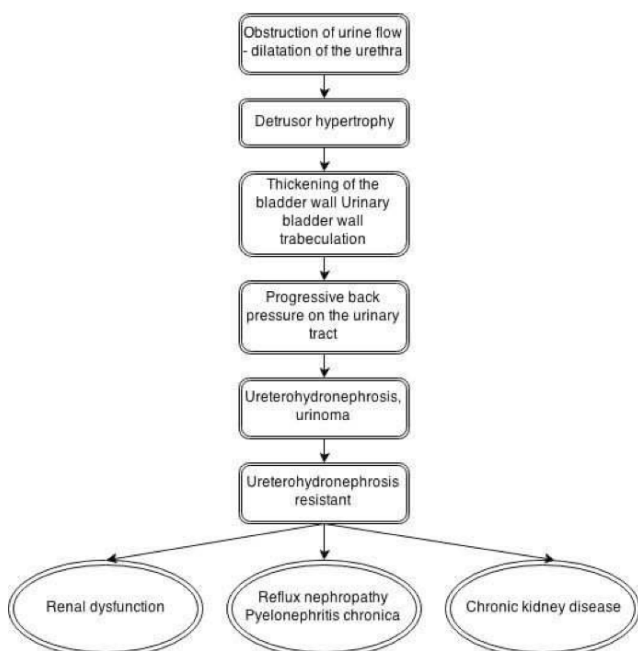
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Introduction

In children, congenital obstructive uropathies are the cause of 30–60% of chronic kidney disease (CKD) cases. Among these, posterior urethral valve (PUV) in boys is the most prevalent. Obstructions in the urinary tract lead to its functional and anatomical changes, and then to the development of CKD.^{1,2}

Fetal development of the urinary tract is a very complex process, involving a number of genes.³ The process of nephrogenesis begins between the 3rd and the 4th week of gestation, and according to Hennis et al., the onset of histological changes that lead to PUV formation can be observed already in the 4th week of the fetal life.⁴ Around 95% cases of PUVs result from abnormal insertion of the mesonephric ducts into the cloaca, followed by formation of anomalous ridges or folds.⁵ PUV increases the residual urine volume after bladder voiding. In 1919, Young distinguished 3 types of PUV: type I (folds which originate from the distal edge of the colliculus) – most often observed, type II (folds, originating from the proximal edge of the colliculus), and type III – with the worst prognosis (a membrane with a central hole, not linked with the colliculus).⁶ Modern therapeutic procedure involve endoscopic valve ablation (through urethra) shortly after the birth, but in some cases, especially in prenatal babies with too small urethras, temporary vesicostomy may be necessary.^{7,8} Even early surgical intervention is usually insufficient, and patients with PUV develop valve bladder syndrome (VBS); in 25–45% CKD will develop eventually.⁷ Obstruction of the urine flow resulting from PUV leads to various, sometimes life-threatening consequences (Fig. 1).

Fig. 1. Consequences of the obstruction of the urine flow



Valve bladder syndrome (VBS) was described by Mitchell (1982) as a complication of PUV, resulting in a combination of persistent upper urinary tract dilatation, hypertrophy of the bladder walls, vesicoureteral reflux, and hydronephrosis. All these changes may lead to various kidney injuries and compromise urinary bladder functions.¹ Patients with VBS demonstrate considerably reduced contractility of detrusors, increased bladder compliance and a higher post-voiding residual (PVR). These parameters are described as the risk factors of dilatation of the upper urinary tract. Phases of valve bladder development can be described as follows: initially, in infants, the bladder is growing in mass, has small capacity and increased contractility. It is usually almost empty, and the voiding pressure is high.⁹ In the next 3 years from valve ablation, in compensated stage, volume of the bladder increases, and the pressures are maintained above the control level, because of abnormality in smooth muscles, contractility gradually decreases leading to a bladder instability.⁹ In the last phase, decompensation of bladder functioning is clinically apparent; the bladder capacity progressively increases, but bladder compliance, contractility and emptying are decreased (so called myogenic bladder insufficiency).¹⁰

Another serious complication of PUV exerting adverse effects on fetal development is oligohydramnios, which can cause the death of the fetus.

In almost two-thirds of the children with PUV, CKD will develop, and 11–51% of this population will progress to ESRD around the age of puberty.¹¹

Optimal diagnostic and therapeutic procedures that will reduce the complications of PUV are of vital importance. For example, Bhadoo D. et al. proposed the “step ladder” of PUV treatment:

- valve ablation/vesicostomy,
- USPCN: Ultrasound guided percutaneous nephrostomy,
- ureterostomy.

In the analyzed cases, the primary endoscopic valve ablation was the most common initial procedure. Chronic renal failure was seen in 42.7% of the patients. In their study, the high prognostic significance of initial serum creatinine, PRA levels and GFR for developing CKD in patients with PUV was confirmed.¹²

CKD risk factors

Many prognostic factors for future renal function in patients with PUV have been proposed.^{1,2,8} A systematic monitoring of these indicators is necessary for the appropriate selection of treatment methods and the time of their implementation, optimal for delaying the onset of CKD or slowing its progression. Most important of those prognostic factors include: the age at the time of diagnosis, the serum creatinine level, considerable

Table 1. The risk factors of developing chronic renal disease (patients before and after PUV ablation)

Laboratory findings	Kidney ultrasound image	Patient's history	Co-existing anomalies of urinary tract	Surgical procedures	Urodynamic tests
nadir serum creatinine ≥ 1.0 mg/dL	kidney dysplasia (small renal volume (<3 percentile))	age at presentation before 1 year	bilateral vesicoureteral reflux, hydronephrosis	late surgical intervention	excessive bladder contraction and low bladder capacity in infants
reduced eGFR at 1 year of age < 90 mL/min/1.73 m ²	kidney scarring	urinary incontinence at the age > 5 years	bladder dysfunction – low susceptibility, detrusor overactivity, urinary retention		increase in bladder capacity, resolution of excessive contraction, unstable bladder function over 3 years from the valve ablation
creatinine > 1.0 mg/dL at diagnosis of posterior urethral valves	small RPA (renal parenchymal area) – RPA's growth of 1 cm ² correlated with a decrease in the risk of ESRD, the cut-off point in the study assumed at the size of 12.4 cm ² (boys with RPA < 12.4 cm ² showed progression to ESRD 10 times more likely than those with RPA ≥ 12.4 cm ²)	growth impairment			progression with age to a large myogenic insufficient bladder
high concentration of urea nitrogen in blood serum	increased echogenicity	over 3 episodes of febrile UTI			
proteinuria	abnormal distribution of core / kidney cortex ratio	hypertension			
metabolic acidosis					

vesicoureteral reflux, renal dysplasia, and the presence or lack of the bladder dysfunction (Table 1).

A separate problem concerns renal prognosis for patients diagnosed in utero with PUV. Some authors suggest the important role of fetal urine analysis. According to Lipitz et al., sodium, calcium, and beta 2-microglobulin in fetal urine were the best predictors for fetal survival.¹³ Muller et al. have assessed that the prediction of postnatal renal function can be based on the fetal urinary concentration of beta 2-microglobulin as it was both specific and sensitive test, whereas other parameters lacked either specificity (sodium, chloride, and urea levels) or sensitivity (fetal urinary glucose, phosphorus, calcium, ammonium, and total proteins).¹⁴ Another investigated parameter is fetal serum beta 2-microglobulin, whose concentration might be independent from gestational age.¹⁵ Nevertheless, there is still no consensus over the value of fetal urine assessment in CKD prognosis. For example, Morris et al. in their systematic review defined calcium and sodium levels as the most accurate predictors, and at the same time stated that current research is insufficient to determine the optimal, biochemical prognostic markers of postnatal renal function in PUV patients.¹⁶

Age at the time of diagnosis

The diagnosis of PUV at an early age is associated with a poor prognosis of further renal function and high incidence of CKD development. It is possible that this association is due to the fact that early diagnosis is often a result of more severe anatomical anomalies.^{7,9,17,18}

Nadir serum creatinine concentration

It is accepted that the nadir serum creatinine concentration equal to or higher than 1 mg/dL in the 1st year of life demonstrates a strong association with a higher probability of developing CKD and worse prognosis of its progression to ESRD.^{7,9,17–19} Some researchers postulate the importance of high serum creatinine concentration on the diagnosis of PUV as a negative prognostic factor of developing CKD or nadir serum creatinine concentration after valve ablation.^{20,21}

Glomerular filtration rate

Also, the decline in eGFR in the 1st year of life is widely reported as a negative prognostic factor of developing

CKD.^{22,23} In 2003, Osama demonstrated that when the clearance of creatinine was lower than 60 mL/min/1.73 m², the prognosis for renal failure in the future would be at approximately 50%, while for creatinine clearance above 90 mL/min/1.73 m², the incidence of renal failure would decrease to 27%.¹⁷

Some other factors are also considered in assessing the risk of developing CKD in the future or its progression to ESRD. The most often mentioned amongst them are: the existence of renal dysplasia, vesicoureteral reflux, various bladder dysfunctions (reduced contractility of detrusors, decreased bladder compliance, etc.), proteinuria and hypertension, more than 3 episodes of urinary tract infections (UTI) and late surgical intervention.^{1,7,9,17–20}

Prenatal diagnostic strategies

Choosing an appropriate diagnostic path is of extreme importance in patients with PUV. Early diagnosis is necessary for implementing therapeutic procedures that will minimize CKD development in those patients, and reduce the rate of progression to ESRD.

Ultrasound

Ultrasound (US) imaging is used to visualize anatomical anomalies of fetal bladder in the 1st trimester of pregnancy and dilatation in the urinary tract from 18th–20th week of gestation. Such findings usually provide an insight into potential pathologies within the urinary tract, and can also be a marker of karyotype abnormalities.²⁴

PUV patients present a certain set of characteristic ultrasound features, mainly a dilatation of the posterior urethra, thickening of the urinary bladder wall (so-called “keyhole” sign) and dilatation within the upper urinary tract. When those features coexist with renal parenchyma pathology, oligohydramnios and pulmonary hypoplasia, identified before the 24th week of pregnancy, they may constitute the reason for in utero surgical therapy. Unfortunately, US imaging is still an imperfect method, with significant limitations. For example, in the prenatal cases suspected of PUV analyzed by Hutton, the anomaly was confirmed after birth in only 42% of the newborns.¹⁰ The keyhole sign in US imaging is not predictive of classic posterior urethral valves and the diagnosis of “PUV” is sometimes made without positively identifying valve tissue. Type I PUV cannot be differentiated from other forms of obstruction (such as urethral diaphragm, atresia, etc.) by traditional ultrasonography.^{18,25} Some ultrasound specialists recognize that the resolution of today’s ultrasonography is insufficient to provide a more precise anatomical diagnosis. Following a series of observations in 2009, Bernardes LS et al. found that the classical prenatal ultrasound, used to diagnose PUV, showed high sensitivity but low specificity.²⁵ Currently, the best

diagnostic indicators of PUV in prenatal US imaging are: the increased thickness of the bladder wall and the dilatation of the bladder. Another US measurement is longitudinal bladder dimension (associated with a poor renal prognosis when it exceeds 15 mm).^{11,26}

Assessment of fetal renal function

Fetal urine analysis is being currently investigated as an excellent diagnostic tool for predicting the future renal function in patients with PUV. One of the laboratory values used as a predictor is the urinary sodium concentration, which helps to determine the function of renal tubules. The normal value for fetal urinary sodium concentration is below 90 mmol/L between the 20th and the 30th week of gestation. Sodium levels in urine above 100 mmol/L have been found to indicate a condition threatening fetal life (usually either renal or pulmonary failure).^{13,27}

Beta 2-microglobulin is freely filtered by the normal fetal glomeruli and nearly in 100% reabsorbed in the proximal tubules, thus it can be useful as an indicator of fetal glomerular filtration rate (GFR). It also has a predictive value as to postnatal GFR. Beta 2-microglobulin detected in the urine suggests an impairment in renal tubules function.^{13,20,27} Other prognostic factors in fetal urine analysis, such as its specific gravity, osmolality, and the excreted volume have been defined by Glick et al.²⁸

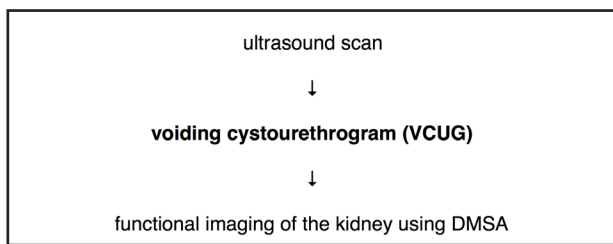
Tests assessing the beta 2-microglobulin in fetal urine and N-acetyl-beta-D-glucosaminidase (NAG) concentration in serum have been recently used to evaluate the degree of damage of renal parenchyma (their concentration is proportional to the extent of damage). The concentration of beta 2-microglobulin above 4 mg/L and cystatin C levels above 1 mg/L, and the NAG levels above 6 mg/dL are thought to be poor prognostic factors for postnatal renal function.^{13,20,27,29,30}

Postnatal monitoring

Voiding cystourethrography

In male newborns with prenatally diagnosed hydronephrosis and a “keyhole” image in US examination, associated with a high PUV probability, a prompt, extended diagnostics of the urinary system is recommended. Cystography has been established as a diagnostic “golden standard” (Fig. 2). For example, performing voiding cystourethrography (VCUG) in these cases (prenatally diagnosed hydronephrosis with high probability of vesicoureteral reflux or lower urinary tract pathologies) has been recommended by the Society for Fetal Urology and Canadian Urological association.³¹ VCUG can be performed without anesthesia. It reveals residual urine and vesicoureteral reflux, and is also useful in the assessment of detrusor and bladder neck activity.^{7,32}

Fig. 2. Golden diagnostic standard for patients with prenatal suspicion of PUV



Urodynamic studies

Pathophysiological changes leading to urinary bladder dysfunction and deterioration in upper urinary tract functions in patients with PUV seem to occur even despite an early diagnosis and valve ablation.

Urodynamic tests in children are employed as an effective way to establish the urodynamic pattern of the bladder, and implement appropriate treatment. In their study involving patients with PUV, Capitanucci et al. compared the usefulness of noninvasive urodynamic evaluation vs invasive urodynamics in detecting lower urinary tract dysfunction and preventing CKD development. They have found similar effectiveness and safety of both approaches. Some patients experience strong discomfort during invasive urodynamic studies, and many decline further procedures. This gives the noninvasive approach an advantage. There are no clear guidelines regarding the frequency of performing urodynamic studies. However, it seems to be reasonable to perform them with each change in employed therapeutic method.³³

Late diagnosis of PUV

Most of the children with PUV are diagnosed before birth, during a prenatal ultrasound. Sometimes, however, there are no symptoms at this stage, so the disease can go undiagnosed into childhood. Zornoza et al. described 8 cases of late diagnosed PUV in children between 1 and 14 years of age. Five patients had symptoms related to voiding dysfunction, and the other 3 were diagnosed incidentally during cystoscopy performed for another reason. All patients were operated, and after a 20-month follow-up no stenosis were diagnosed. Voiding cystourethrogram (VCUG) is a much more specific method for diagnosing PUV than an ultrasound. Diagnosis can also be made by cystoscopy, where a small camera is inserted into the urethra for direct visualization of the posteriorly positioned valve, and this method is recommended by Zornoza et al. in any case of urinary retention.³⁴

An urodynamic investigation of valve bladder syndrome is very important. Wen et al. reported in an urodynamic study, performed in 2 groups of patients (less than 1 year and more than 1 year after urethral valve fulgura-

tion), that PVR and maximum bladder capacity (MBC) increase with age after the procedure. Multiple bladder dysfunctions can be diagnosed accurately using urodynamics.¹⁹

Management strategies

An early diagnosis of PUV with its complications, including VBS, and the application of the right treatment at the right time is of key importance for the prognosis, and may prevent or delay CKD in the future.

Unfortunately, even after successful valve ablation some degree of bladder dysfunction will develop in most of the patients. This is true even for PUV patients who have been surgically treated at a very early stage of the disease.^{7,19} Therefore, patients with PUV require constant monitoring, also after surgical procedure, in order to detect symptoms of VBS early enough to undertake possible preventive methods.

Multi-center observations estimate the incidence of CKD in the population of boys with PUV at 10–30.4% (in the age group from the 1st month of life up to 18 years).^{18,35} Early diagnosis due to prenatal examinations (diagnostics imaging, laboratory assays, etc.) together with timely surgical interventions in utero have led to a significant decrease of mortality, and improved overall health in this group of patients.^{20,29} Nevertheless, we still lack the clear guidelines for the best type of surgical procedure, and each case needs individual assessment of possible risks and gains.

Strategies of limiting the risk of developing CKD in patients with VBS include diagnostic imaging, laboratory tests and therapeutic procedures. The latter are not only surgical interventions (including in utero), but also pharmacotherapy and other procedures, which mainly aim at reducing the residual urine in the bladder.

Treatment possibilities

Modern surgical techniques allow for PUV ablation performed in utero. In that case the procedure carries a significant risk of complications, such as fetal injury or even fetal or maternal death. For example, Sananes N. et al. reported 2-year outcomes after therapeutic fetal cystoscopy with ablation of PUV, where only 57% of infants survived.³⁶ This is why intrauterine surgeries are reserved for exceptional cases (Fig. 4, 5). There is still a lack of consensus as to the advantages of intrauterine intervention over surgery after birth.²⁹ Intrauterine treatment currently is limited to cases of fetuses with oligohydramnios and diagnosed before the 2nd trimester.^{10,19} There are 3 possible treatments: amnio-bladder valve, vesicostomy and fetal endoscopic valve ablation, and none of them has definite advantage supported by evidence.⁸

A proper understanding of the molecular pathways, which are activated in damaged cells of the bladder wall, allows for appropriate pharmacological intervention in order to improve its function.^{4,22} Modern pharmacotherapy in VBS uses drugs like:

- cholinolytics (e.g., oxybutynin – 0.2 mg/kg/24 h), which decrease hyper-tractility of the bladder; therapy should be started right after valve ablation, even when urine incontinence is not presented; their use in the long term leads to a myogenic bladder failure – then it is recommended to use the CIC (clean, intermittent catheterization), but sometimes, after discontinuation of cholinolytic, the bladder function normalizes on its own,^{9,18,19,37,38}
- alpha-blockers (e.g., terazosin – 0.25–2 mg), which help in bladder voiding; their use is particularly advisable when obstruction in bladder neck is suspected cause of ineffective voiding.¹⁰

Other drugs that are being tested in patients with VBS are aimed at reversing histological changes in the bladder (mainly ACEI and various growth factors inhibitors).³⁹

Non-pharmacological procedures used in VBS management include:

- timed bladder voiding, double or even triple bladder voiding;^{10,18,38,39}

Fig. 3. Management of urine incontinence in VBS

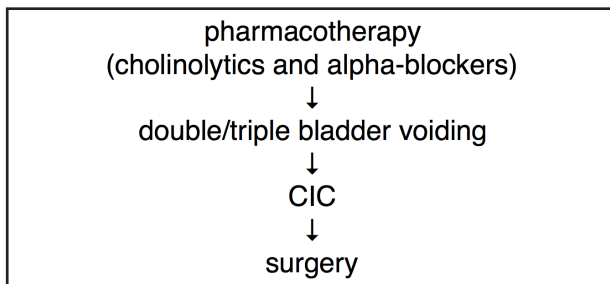


Fig. 4. Steps to take before choosing the intrauterine intervention

- **determination of fetal karyotype (fetuses with obstructive uropathy are frequently diagnosed with chromosome abnormalities)**
- **a close ultrasound examination in order to detect other co-existing defects, including heart defects**
- **ultrasound evaluation of fetal urinary tract blockage (dilatation) and parenchymal architecture of the kidney**
- **amniotic fluid volume assessment**
- **doppler ultrasound of the fetal renal arteries**
- **fetal urine analysis**

- clean, intermittent catheterization (CIC) that allows for effective emptying of the bladder, also preventing urinary blockage and reducing risk of recurrent urinary tract infections;^{9,10,18,22,39,40}
- as recurring urinary tract infections (UTI) are one of risk factors for CKD development in VBS patients, some authors concentrated on assessing various preventative methods. The clear rules of antibiotic preventive therapy has not been established, some recommend trimethoprim 1–2 mg nightly dose until vesicoureteral reflux recedes or age of 4–5 years.^{10,37} Interestingly, many authors quote arguments of the positive effects of circumcision in UTI prevention in children with PUV;^{11,37}
- some other methods for reducing urinary retention in the bladder include pelvic floor muscles exercise and Valsalva maneuver.^{10,18}

When all of the methods mentioned above are insufficient in reducing urine retention and improving bladder voiding, surgical procedures are performed:

- bladder augmentation, traditionally enterocystoplasty, but recently more popular ureterocystoplasty, which retains histological structure of the urinary tract;^{9,10}
- high ureter diversion (various versions: vesicostomy, percutaneous ureterostomy, pyelostomy, nephrostomy, etc.) is controversial due to the lack of strong evidence that it can prevent CKD;⁹
- Mitrofanoff appendicovesicostomy is one of the treatments of the valve bladder syndrome that allows patients clean intermittent catheterization and overnight drainage when catheterization is impossible. King et al. reported that this way of treatment can achieve significant improvements in decreasing hydronephrosis and urodynamic parameters of bladder dysfunction. However, it does not prevent renal deterioration and progression to CKD.^{1,10,21}

All treatment possibilities listed above are illustrated in Fig. 3.

Performing the valve ablation alone, without urodynamic follow-up, is inappropriate. Urinary diversion is still a very popular procedure, but recent studies suggest that in most cases in which diversion is considered,

Fig. 5. Biochemical markers of good prognosis

- **Na⁺ < 100 mEq/L**
- **Cl⁻ < 90 mEq/L**
- **osmolarity < 210 mOsm/L**
- **β2-microglobulin < 4 mg/L**
- **total protein < 40 mg/dL**
- **Ca²⁺ < 8 mg/dL**

those same patients can be treated with proactive urodynamics and anticholinergic therapy achieving similar results. It is still unclear if growth factor inhibitors or angiotensin converting enzyme inhibitors have a role in preventing or reversing the histological changes of the valve bladder.³⁹

Summary

PUV is a congenital, obstructive uropathy leading to the valve bladder syndrome, which in turn results in the development of CKD. Active urodynamic monitoring of the PUV patients plays a significant role in the prevention of bladder dysfunction, CKD development and its progression to ESRD.

Early diagnosis is currently possible even before birth (thanks to ultrasound, fetal urine analysis and some biochemical tests of fetal blood). At later stages cystography and urodynamic tests are essential to monitor the PUV patients, and determine the risk of developing CKD.

The therapeutic methods for preventing or minimizing VBS vary from surgical approach (which can be implemented in utero) through some mechanical procedures (such as timed bladder voiding and CIC) to pharmacological management.

Due to the fact that cytological changes in the urinary tract, observed in children with PUV, are irreversible, medical intervention ought to be carried out with due haste after the diagnosis, but prenatal procedures, carrying a high risk of complications, are still reserved for the minority of cases.

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