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# The Role of Radiographic Imaging in Diagnosis and Follow-up of Vesicoureteral Reflux: Review Article

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Primary vesicoureteral reflux is a basic influencing for urinary tract infections in children. The basic technique for the diagnosis of vesicoureteral reflux is voiding cystourethrography, accompanied with cystoscintigraphy. Voiding cystourethrography has the benefit of only minor irradiation. However it does no longer permit the morphological assessment of bladder and vesicoureteral reflux grading. Colored-Doppler cystosonography with echocontrast is a currently delivered technique for imaging vesicoureteral reflux. The purpose of our study is to explore the role of Radiographic Imaging in diagnosis and follow-up of vesicoureteral reflux.
**Method:** A systematic review was carried out, (including PubMed, Google Scholar, and EBSCO) of imaging modalities used to detect or evaluate vesicoureteral reflux disease. The found articles were screened by titles, and abstracts. No software will be utilized to analyze the data. The review was performed by the group members and each verified by at least two, to ensure the validity and minimize the mistakes.
**Results and Conclusion:** Colour-Doppler cystosonography, due to the nonexistence of ionizing radiations, has great benefits, mainly in cases requiring continued or prolonged monitoring. In spite of practices stated in the literature, this procedure has a role in the diagnosis of vesicoureteral reflux. Our group chooses colour-Doppler cystosonography for the follow-up of medium-severe

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grade vesicoureteral reflux previously diagnosed by radiology and/or scintigraphy. Cystoscintigraphy is used only to confirm cases resulting negative at ultrasonography.

*Keywords:Radiographic imaging; different modalities; vesicoureteral reflux disease.*

## 1. INTRODUCTION

Vesicoureteral reflux (VUR) is a communal health problem in children which is the retrogressive urine flow from the urinary bladder to the upper urinary tract. VUR could be asymptomatic or concomitant with severe nephropathy. It is frequently has a genetic origin and has an inclusive prevalence of 7.0% in infants presenting with fever and a pooled prevalence of 7.8% among children with urinary symptoms [1]. Early diagnosis and timely treatment of VUR can save the kidneys.

A decrease in the ratio is one of the causes of urine vesicoureteral reflux (VUR). Other causes of VUR including the ectopic ureteric opening, immature bladder dis-coordination, or bladder dysfunction.

Vesicoureteral reflux (VUR) is the cause of about one-third of urinary tract infections. The association of these two pathologies can control reflux nephropathy, which can be complex by inducing hypertension in 30% of cases and even renal failure in 20% [2].

Urinary tract infection (UTI), prenatal/postnatal urinary tract dilatation, dysfunctional voiding, bladder outlet obstruction, neurogenic bladder, dysuria, hematuria and trauma are the most common indications for VUR. This finding usually prompts a radiographic investigation in an effort to identify which children are at risk for recurrent infections and renal damage, which allows a therapy to be instituted to prevent future illness or injury [3].

There are many radiographic imaging modalities was described to diagnose vesicoureteral reflux, however, voiding cystourethrogram (VCU) is an important method of diagnosis. The presence of VUR was used to guide major management decisions. The radiographic approach relies on a voiding cystourethrogram (VCUG) to determine if VUR or other lower tract anomalies exist in such previous cases, along with a renal-bladder ultrasound (RBUS) to detect renal parenchymal defects or dilation suggestive of obstruction [4]. Clinical presentation of the case and VUR determine the treatment plan.

There are five grades of VUR which differs from each other in the symptoms and the suitable treatment [5].

The international grading system of VUR:

Grade 1: Reflux only into the non-dilated ureter.
Grade 2: Reflux into the ureter and the renal pelvis without dilatation.
Grade 3: Reflux with mildly dilated ureter and pyelocalyceal system.
Grade 4: Reflux with the tortuous and moderately dilated ureter with blunting of renal fornices. The papillary impression is preserved.
Grade 5: Reflux with the tortuous and severely dilated ureter, dilatation of pyelocalyceswith loss of fornices, and papillary impression.

## 2. OBJECTIVES

To assess the role of different Radiographic imaging modalities in the diagnosis of vesicoureteral reflux disease.

### 2.1 History of Diagnosis of Vesicoureteral Reflux

Previously, urodynamic tests have been considered the common method for diagnosing most conditions of the lower urinary tract such detrusor overactivity (DO), bladder outlet obstruction (BOO) and Vesicoureteral reflux (VUR). However, with increasing morbidity, there has been a search towards non-invasive techniques such as ultrasound, computed tomography (CT), PET, magnetic resonance imaging (MRI), with the potential of becoming the mainstay diagnostic tools for LUTD. Furthermore, clinical assessment of the urethral symptoms is challenging and often requires further evaluation with imaging. And lately, VUR was known as the gold standard for diagnosing VUR [6].

### 2.2 Different Radiographic Imaging Techniques in Diagnosis of Vesicoureteral Reflux

Imaging modalities used in UTI diagnosis including ultrasound (US), voiding cystourethrogram X-ray (VCUG), magnetic

resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are chosen according to the case and are used to visualize the characteristic structures of the LUT to indicate the abnormalities.

US is the commonly used technique in daily practice, to evaluate LUTD. The utilization of MRI for voiding dysfunction however remains limited, but several clinical studies have already shown its potential in the benign prostatic hyperplasia (BPH) and diagnosis of stress urinary incontinence. Also, PET and fMRI of the brain have made it possible to study supraspinal control of the LUT, in the light of LUT being subjected to a complex neural control mechanism.

In case of VUR, the first-choice technique for the diagnosis is voiding cystourethrography (VCU), whoever, many previous studies have suggested ultrasonography (US) as an effective diagnostic procedure for identifying VUR; the use of microbubbles has improved this technique. [7,8] The differentiation of the different five stages of VUR is easy using this technique and specially to confirm the excellent results in the diagnosis of severe grade reflux [9,7].

The application of this way is performed with a protocol involving transurethral catheterization followed by the introduction of saline solution containing air bubbles to the bladder, to be easily detected by US. The air bubbles is created by either shaken the saline in the container before administration or rapidly flushed in and out of a syringe; the limited stability of the bubbles, however, means an extremely brief ultrasonographic observation time.

Another highly sensitive technique is radionuclide cystography, which requires the introduction of radionuclides, rather than of iodinate contrast medium, in the bladder through transurethral catheterization; it has the advantage of very low irradiation of the patient, but it lacks spatial resolution. [8] Later, Atala in 1993, established the Cystosonography (CSG) thechnique, which is an ultrasonographic technique. [10] This technique has the advantage of more stabilized microbubbles, thus allowing a prolonged observation time.

Other studies have been carried out to evaluate and optimize this technique, leading to promoting but not yet recorded results [11,12].

A previous study done by Darge et al. [13] have recently compared the usefulness of voiding US of the bladder and retrovesical space with echo-enhancement with that of VCU (1999).

Voiding ultrasonography is non-radiating and has undergone significant improvements recently and remains the gold standard in reflux diagnosis but is invasive and submits the child to ionizing radiation. Developing technologies need improvements and further research before they may have a role in significantly decreasing voiding cystourethrography use or replacing it completely.

## 3. VOIDING CYSTOURETHROGRAM

### 3.1 Preparation

Voiding cystourethrogram (VCU) requires patient participation for voiding (in toilet-trained children and adults). The performing radiologist or assistant should counsel the patients or their parents. Stress and anexity are the most common conditions affect the patients, so distraction and comfort are common non-pharmacological methods to decrease the stress in the children. The anxious children often require sedation. Midazolam is a commonly used sedating drug for VCU [14].

### 3.2 Technique

For voiding cystourethrogram (VCU), The experienced nurse or radiology assistant catheterize the patient with aseptic precautions. The anesthetic gel reduces pain and distress. The size of the catheter is usually according to the patient's age. A smaller caliber catheter is in patients with a history of urethral stricture or recent surgery. It is useful for its easy passage into the urethra. Avoid excessive length insertion in the bladder to prevent intravesical looping of the catheter. Drain the bladder before the study. Water-soluble contrast is used to fill the urinary bladder. It allows visualization of the bladder under fluoroscopy. Connect the bottle of water-soluble to the catheter via a tube. Place the bottle at a height to allow a gravity drip of contrast. Place the bottle at a lower height in patients with recent bladder surgery to maintain lower pressure filling [5].

Fluoroscopy is performed to monitor contrast reflux from the bladder into the ureter or upper urinary tract. Perform pulsed fluoroscopy to monitor contrast filling into the bladder. Use collimation to minimize radiation dosage to the

patient. Fill the bladder retrogradely until voiding occurs (in non-toilet trained patients). Fill the bladder in toilet-trained children and adults until they want to micturate [15].

Obtain fluoroscopic images of the bladder in anteroposterior, right anterior oblique, left anterior oblique, and lateral projections during early filling and when it is distended with contrast. Reflux can occur during, before, or after voiding.

Perform cyclical voiding to increases the possibility of VUR detection [16].

Fill the bladder with contrast and repeat the voiding cycle for 2-3 times before removing the catheter. Cyclical VCU is routinely performed in children younger than one year of age because they void at a lower volume. It is also performed in patients with a high probability of having VUR (e.g., recurrent urinary tract infection, Hutch diverticulum, and pyelonephritis). Do not repeat a cycle if VUR occurs during the first filling. Cyclical voiding helps in urinary tract dilation. There is often dilution of refluxed contrast when it is mixed with unopacified urine in the dilated ureter. Diluted contrast is sometimes difficult to visualize under fluoroscopy, and grading is incorrect in such situations. Cyclical filling avoids the dilution [16].

Voiding cystourethrogram (VCU) is also useful for postoperative evaluation of the urinary tract.

### 3.3 Renal-bladder Ultrasound

RBUS is the most common primary intervention for a child with febrile or afebrile UTI. It is save because it does not use ionizing radioactivity and it is generally well accepted since it is painless and noninvasive. It can rapidly and generally show the urinary tract anatomy. However, many children with congenital urinary tract irregularities are now identified with prenatal ultrasounds and undergo medical or surgical interventions before a FUTI may occur [17].

RBUS is often seen as an important part of urologic consultation or investigation; but for infants with hard prenatal care, it may offer only an insignificant benefit and it was reported that RBUS only retains a sensitivity and specificity of 40% and 76%, respectively for VUR [18].

Although it is widely available, it has been previously shown that RBUS results also do not significantly alter the treatment plan for a patient in the same way as an abnormal DMSA scan or VCUG [19].

RBUS is a technician dependent technique and it does not provide a quantitative assessment of renal function and it is not sensitive enough to detect all scarring. On the other hand, it is often comforting to the family to have a safe, noninvasive exam that grossly reveals the condition of the kidneys.

With the reduced use of ionizing radiation and several guides that rely on RBUS for other studies, many studies have been published which assess the accuracy of RBUS as a genitourinary abnormal screening test (including VUR). A retrospective cohort of 2,259 patients under age 60 months who have both VCUG as well as RBUS for a long FUTI history was the largest of these studies. The participants received the two studies on the same day in this population.

The achievement of one study did not depend on the other's results. Whatever criteria were used for positive or negative tests, RBUS had poor sensitivity and a low positive predictive value. Only the highest grades of VUR showed negative prediction values. There was high specificity (up to 97%), but only when sensitivity was low (<10%). A "normal" RBUS doesn't therefore rule out important VUR grades. Likewise, a "positive" test is not pathology predictive [20].

The authors therefore conclude that a full-scale anatomic information on one patient requires both RBUS and VCUG studies.

This population was assessed as to whether the use of the combination of "positive" RBUS findings, including renal dilation, urothellial thickening, ureteral dilation, parenchymal abnormalities and bladding, could be used to determine sophisticated prediction models. These various findings cannot be combined into a predictive model that accurately screes for abnormalities detected with VCUG despite the use of multivariate logistic models and neural network machine learning algorithms. They found that RBUS had no predictive value even for VUR of the highest standard and that this was therefore a poor screening test [21].

Instead of providing appropriate isolation detail, the authors once again concluded that the RBUS study complemented a VCUG.

### 3.4 Renal Scintigraphy

DMSA is applied to replace intravenous urogram for kidney and chronic renal scars. The key concept of the 'top-down' method is to identify which kidneys with an early DMSA scan are vulnerable to further injury. A standard DMSA scan prevents the need for a VCUG to be ordered. This isolates the most risky VUR cohort and reduces the need for extensive VCUG monitoring. This viewpoint focuses on the presence of renal parenchyma instead of VUR, which stimulates the damage sustained [22, 23]. Further DMSA scanning shows new wounds at pre-inflammatory sites. However, it is helpful in exploring the effect of the abnormality, not the presence of the causing abnormality.

Cochrane Database of Systematic Reviews carried out the 2016 Meta-Analysis of publication studies to assess if RBUS or DMSA had higher precision in the diagnosis of any grade VUR or high grade VUR (grade III-V VUR), to make them a screening tool. In the sense of a cultured FUTI, the authors examined only studies where children were tested both for the index (RBUS or DMSA) and for VCUS.

For the target conditions, summary sensitivity and specificity estimates were created. Between the studies there was a significant heterogeneity and none individually indicated a high value. The authors found that RBUS and DMSA had not been shown to be accurate enough to recognize either VUR or high-grade VUR grades. Although the summary sensitivity of a negative DMSA trial was 0.93, the specificity was poor (0.44), which reduced its usefulness as a VUR test [24].

Considering the facts, it should be remembered that the etiology and importance of scars on initial DMSA or RBUS is not being agreed. Congenital dysplasia may be responsible for cortical deficiencies instead of new infection and/or VUR injuries. An abnormal DMSA research can be conducted in newborns with prenatal hydronephrosis and without an abnormal UTI history [25].

Like VCUGs, an irregular scan with DMSA could mistakenly isolate a cohort of children as vulnerable to renal cure when their defects indicate static congenital dysplasia. Nevertheless, at least 50% of patients with inflammatory evidence of DMSA at FUTI have chronic renal scarring [26]. A subset of children would be subject to over-treatment in either case. However, surveillance morbidity is probably higher in a child who is suffering from clinically insignificant VUR than that of a child who has a congenital dysplastic kidney.

Both VCUG and DMSA scans expose children to potentially adverse, ionising radiation. A greater dose of radiation to the gonads has previously been found to be transmitted by VCUGs [27]. But the radiation dose of DMSA is 10 times higher than that of a pulsated fluoroscopy, commonly used in most VCUG examination halls [27].

Radiation is also spread around the entire body during a DMSA scan, at a kidney concentration, while the energy is concentrated on the pelvis during fluoroscopy. This exposure may be increased by serial examinations. The additional disadvantages of the DMSA scan include the need for intravenous and possibly sedative access, lack of availability at all of the facilities, inconsistent and delayed examination interpretation and longer test time (1-3 hours). The urethral catheterization requirement, which can lead to a problem for patients and their families, is a major restriction to VCUG.

Thus, the search continues for alternative technology that can overcome the risks and flaws outlined above.

### 3.5 Emerging Imaging Technology

The technology is available for clinicians as the diagnostic model for FUTI evolves. Difference in diagnostic capacities and the perception of disease processes can be greatly altered by the radiographic choices at the horizon.

In one study, MRU can supply both anatomical and functional data. Congenital renal dysplasia can be distinguished from acquired MRU renal damage due to the enhanced spatial and contrast resolution [28].

Reports have shown an association between VUR grade and the degree and volume of renal parenchymal damage detected by MRU [29]. In a retrospective review of 114 patients with VUR and 21 non-refluxing controls, MRU was able to detect a renal size discrepancy between the 2 groups. This size discrepancy persisted in the comparison of contralateral non-refluxing kidneys with non-refluxing controls and occurred in the absence of focal scarring ($p<0.0001$). This data supports the notion that patients with VUR can have abnormal embryological development or hypoplasia before birth and the first insult of a FUTI.

Alternatively, the contralateral non-refluxing kidney may be impacted by bilateral pyelonephritis initiated by the refluxing kidney. The etiology is still unclear, but the association between VUR and FUTI could be characterized more completely if MRU assessment is included in future studies.

A thorough assessment of renal morphological anomalies and testing for VUR without irradiation risks would be ideal. As shown in many recent studies, magnetic resonance imaging (MRI) is able to do both. In one of the earliest studies of intraurethral Gadolinium magnetic resonance voiding cystology (MRVC), the identification of VUR by VCUG and renal damage by DMSA has been excellent [30], and additionally the detection of additional Urinary Tract abnormalities has contributed to this technique.

This approach was refined in a study on interactive MRVC (iMRVC), which involves using a pulse sequence and rapid switching between views to permit sustained dynamic imaging of the urinary tract [31]. A feasibility study in unsedated infants was conducted on 12 patients with a first FUTI or defects on early postnatal ultrasound [31]. Five children who used iMRVC compared to three who used traditional VCUG identified VUR (sensitivity 100 percent , specificity 83 percent for iMRVC). However, one of the limitations is that a single cycle VCUG analysis was followed by the iMRVC tests.

With successive rounds of bladder filling, VUR detection is known to increase. The iMRVC studies obtained adequate pictures of the urethra and the method was refined during the test, which reduced the time needed by the VCUG by 60 minutes to 20 minutes [31]. Intravoxel incoherent motion (IVIM) diffusion weighted imaging in the MRI system is the latest technique reported. Just one report on 83 kidneys in 57 patients has been published to date. The recorded accuracy of 78 percent (sensitivity 0,81 and specificity 0,77) was found by a particular index measures of IVIM infusion and diffusion parameter [32]. This is a small but successful research, which requires a large population to validate and assess. This procedure is considered non-invasive because it needs no contrasting media or catheterization and is free of ionizing radiation just like any other MR techniques.

Although these test modalities provide elegant and functional structural features, they are expensive, require sophisticated processing techniques, and may require sedation in young patient populations. In MRU studies, contrast agents are associated with the so-called nephrogenic systemic fibrosis and can increase the danger to chronic kidney disease patients [28].

Maybe these new technologies can help to detect the association between VUR, FUTI and renal parenchymal damage in a research setting. Sadly, the right algorithm or technique for studying a patient with FUTI is not yet explained. In terms of clinical practice, study can be supported by the need for new imagery modalities, as the present era is characterized by the rapid implementation of new technology.

Ultrasound can have a revival in some centres if you return to our starting point. In the last 2 years, CEVUS has been refined to increase the precision of harmonic and second-generation imagery contrast agents. The reported CEVUS comparison with VCUG evaluated FUTI children, the upper dilation of tracts or VUR diagnoses [33]. children were evaluated. New or recurrent vura was diagnosed during the examination, but only a fraction of them were identified by VCUG, most of whom were identifiable with cEVUS in the presence of contrast material in the ureter or pelvicalyceal system.
The outcome may be continuous sonographic imaging versus intermittent fluoroscopy. Inadequate imaging or urethra visualization is the bigger downside of this modality. Nevertheless, recent studies show new methods for identifying the posterior urethral valves, the prostatic utricle diverticula and the anterior urethra for children [33]. In both tests, the bladder neck and urethra have been properly visualized. This reflects the use of the same strategies in prior studies [34,35]. Like the MRVC, urethral catheterization is still required in the CEVUS analysis. Sonographers. Sonographers [36].

In contrast to MRVC and MRU, CEVUS is less expensive and may be more accessible to a wider population. However, the techniques are still operator-dependent and require highly skilled sonographers.

## 3.6 Biochemical Markers

"Biochemical markers" are known as biological substances which can be accurately (and reproductively) determined as an indicator of normal or pathogenic conditions. The features of

a biological process should be objective and quantifiable. Biochemical markers should undergo rigorous scientific validation to ensure that any potential combination of disease states is represented in order to be used as a substitute endpoint for a clinical outcome. The statistical relevance or the negative and/or positive predictive value of such a test cannot be proved enough [37,38].

A biomarker that can accurately diagnose disease can be seldom found in isolation, but its importance may be increased if multiplied by other tests. In a broader way, certain biochemical markers can be used to track disease burden or progression, as can the specific cancer, and to predict a reaction to therapeutic intervention [37,38]. In VUR, accurate non-invasive biochemical markers could be identified, which could distinguish between low-risk populations and high risks in order to supplement clinical decision making.

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The collection method is non-invasive, because urinary substances are of particular importance. However, a full review article may be dedicated to urinary bioquemical markers with no reliable scientific validity or contradictory evidence studies [39]. The example of this is serum procalcitonin [40].

A number of non-invasive urinary biochemical markers for reflux nephropathy have been examined in recent publications in children with primary VUR [39]. The systemic reaction of your host to acute pyelonephritis supports the release into serum and urinary tract of molecules and cytokines that can cause or modulate inflammatory response. In children who tend to be susceptible to pyelonephritis even in the absence of VUR, genetic polymorphisms have been found [41,36].

It was proposed that if there is no exclusion marker, maybe biochemical marker panels or combinations would increase clinically [38], but these analytics have not matured to the point of clinical use. The applicability to a clinical setting so far remains restricted by small studies sample size. At the moment, all of these variables cannot be definitely replicated. The area remains in its infancy despite 20 years of research [36].

## 4. CONCLUSION

The present study concluded that Colour-Doppler cystosonography, due to the nonexistence of ionizing radiations, has great benefits, mainly in cases requiring continued or prolonged monitoring. In spite of practices stated in the literature, this procedure has a role in the diagnosis of vesicoureteral reflux.Despite experiences reported in the literature, this technique has a role in the diagnosis of vesicoureteral reflux. The study preferred colour-Doppler cystosonography for the follow-up of medium-severe grade vesicoureteral reflux already diagnosed by radiology and/or scintigraphy.

## CONSENT

It's not applicable.

## ETHICAL APPROVAL

It's not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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