ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 01 | January - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MANAGEMENT OF VESICOURETERAL REFLUX IN ADULTS: A SYSTEMATIC REVIEW

Urology

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ABSTRACT

Vesicoureteral reflux (VUR) is a complex physiological disorder and is usually diagnosed in adults as a continuation of the ailment developed in childhood, which went unnoticed. It is also a common ureteric complication after kidney transplantation and in people with spinal lesions. Vesicoureteral developed from an early age are associated with gene/s, and there is no completely gratified remedy for the disease. The present-day treatment approaches like surveillance, antibiotic prophylaxis, chemical compositions, and surgery are undergoing fast change based on our advanced understanding in medical sciences. Reflux nephropathy (RN) is the renal scarring that is diagnosed in patients with VUR, mostly in association with urinary tract infection. End-stage renal disease is also reported to be associated with primary VUR. The present paper reviews the various options of reflux management in adults.

KEYWORDS

reflex, adults, management, follow up

1. Introduction

Vesicoureteral reflux (VUR) is the abnormal backflow of urine from the bladder to the ureters and kidney from the bladder. It is diagnosed more in infant children than in adults. In the general population, it is present in 1% of the children in North America and Europel. Precise data on the percentage of the population with primary VUR in India are not documented. Vesicoureteral reflux is usually diagnosed after an episode of Urinary tract infection (UTI), and as many as 50% of children with a UTI have VUR 2. The overall incidence of childhood UTI in girls and boys is 8% and 1%–2%, respectively[3]. Its prevalence in adults is not well documented, but it is higher in women, because of their greater propensity for UTIs. In men, even severe VUR may go undiagnosed for a long time. The manifestations leading to a diagnosis of VUR in adults, besides urinary tract infections, are proteinuria, renal failure, and hypertension [4]. Reflux nephropathy (RN) is the renal scarring that is diagnosed in patients with VUR, mostly in association with UTI. End-stage renal disease (ESRD) is reported to be associated with primary VUR in 7-17% patients5. Vesicoureteral reflux leading to reflux nephropathy (RN) is a major cause of ESRF worldwide. Although well described in infants and young children, there are only a few studies on adults with VUR and RN —6. There is conclusive evidence on the inheritance of VUR from parents. Prenatal diagnosis help early recognition and intervention that may reduce the incidence of complications of vesicoureteral reflux, such as pyelonephritis episodes and the development of RN 7. However, RN can occur with UTI in the absence of a VUR, or with VUR in the absence of a UTI[8].

Management of VUR has become more conservative over time as therapies have not been reliably proven to prevent renal scarring. The management of vesicoureteral reflux has undergone a paradigm shift from an open surgical correction at diagnosis in the 70's to conservative medical management over the next two decades and again the early correction using endoscopic therapy 2. In a recent review, it was reported that 80% of children with VUR grow naturally unnoticed 9. Children who have VUR are 1.5x more likely to develop pyelonephritis than those without, and when children with VUR develop a UTI, they are known to have 2.6x risk of having renal scarring compared to children without VUR. Higher grades of reflux are associated with worse renal scarring, with VUR grades 3 and higher having 2.1x more scarring than patients with grades 1-2. VUR diagnosed at older ages is associated with higher rates of renal scarring, with 94% of adult VUR patients having renal scarring, compared to 26% of children under 8 years with VUR. Cornwell et al. (2020) 9 examined the trends seen in this patient population from 1996-2014 and used US census data to calculate incidence. The incidence of patients with new-onset ESRD attributed primarily to RN steadily decreased over time: from 1.9 in 1996 to 0.6 per million in the US population in 2014. When comparing pediatric new-onset ESRD to adult-onset, a non-significant trend was seen with a decrease in the incidence of adult ESRD, but a relatively stable incidence of pediatric ESRD.

This paper reviews the updated status of VUR and RN and their management in adults. Reviews, case reports, original research, and survey studies published in peer-reviewed journals were retrieved through Science Direct, Medline, Medscape, Cochrane, and PubMed databases. University online library facilities were also used to gain full text of selected publications. As far as possible, this review is prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2018.

2. Causes of Vesicoureteral reflux and Reflux nephropathy in Adults

Vesicoureteral reflux (VUR) may have genetic reasons. In its less severe forms, VUR may be asymptomatic, but in 50-70% of cases, it manifests with recurrent cystitis or pyelonephritis. Primary VUR is due to a defect in the valve mechanism of the ureterovesical junction. In physiological conditions, the terminal ureter enters the bladder wall obliquely, and bladder contraction leads to compression of this intravesical portion. The abnormal length of the intravesical portion of the ureter due to a genetic mutation leads to VUR.

Reflux nephropathy (RN) develops as a result of a pathogenetic mechanism unrelated to high cavity pressure or urinary tract infections but due to reduced formation of the normal renal parenchyma (hypoplasia or dysplasia). Abnormal renal parenchyma development is attributable to the same genes that control the development of the ureters and ureterovesical junction. VUR is considered only a marker of this abnormal development, playing no role in scar formation. Currently, the RN is defined as congenital (also called primary), which is a result of abnormal renal development resulting in focal renal dysplasia, or acquired, which results from pyelonephritis-induced renal injury. However, the differentiation of congenital versus acquired RN based on preceding UTI can be arbitrary because the possibility of a preexisting renal scar before the UTI cannot always be ruled out. The acquired RN is seen more often in females, whereas the congenital RN occurs mostly in males. The exact mechanism for renal scarring following UTI is not known. However, it is believed to be mediated by immunological mechanisms, macromolecular trapping, and mesangial dysfunction, vascular alterations, hypertension, and hemodynamic alterations [1]. Renal scarring due to intrarenal reflux occurs mostly at the renal poles because of the presence of extensively fused (compound) renal papillae, which are associated with reflux[8].

3. Diagnosis and Risks Factors of VUR and RN in Adults

The manifestations leading to a diagnosis of VUR in adults are urinary tract infections, proteinuria, renal failure, and hypertension [4]. An increasing number of patients with VUR are also diagnosed during follow-up for antenatally diagnosed renal abnormalities, particularly hydronephrosis. The first presentation of VUR in the adult is rare, but Pereira et al. (2018) [10] reported the case of an adult patient with repetitive uncomplicated pyelonephritis caused by VUR. VUR is diagnosed by a test called a cystogram, and the gold standard for its diagnosis is the voiding cystourethrogram (VCUG), which is graded I to V, grade V being the most severe type 11. VUR certainly has to be corrected in women who contemplate pregnancy[4].

Reflux nephropathy (RN) is the renal scarring that is diagnosed in patients with VUR, mostly in association with UTI. The complications of renal scarring are more common in adults, who may present with recurrent UTI, proteinuria, hypertension, increased Serum Creatinine (sCr), and diminution in glomerular filtration rate. Adult males with RN generally present with hypertension, proteinuria, and renal failure. Females present mostly with UTI and pregnancy-related complications. Males have serious outcomes compared with females. The gender differences in the clinical outcome in adults may be more a result of males having mostly congenital RN compared with acquired RN in females[8].

4. Management of VUR and RN

Management of VUR is controversial and includes antimicrobial prophylaxis, surgical interventions, or surveillance approaches. No evidence-based guidelines exist for appropriate follow-up or the management of patients with RN[8].

Surveillance

Low-grade refluxes may resolve spontaneously without renal scarring if kept infection-free. The chance of spontaneous resolution of reflux is high in children younger than five years with grades I-III reflux. Even higher grades of reflux (grades IV-V) may resolve spontaneously as long as the child remains infection free [12]. However, medicolegal concerns about the risk of kidney damage while a patient is under surveillance have limited the use of this approach[13].

Following a long time observation of 115 adults admitted to the hospital with a history primary reflux and treatment, Köhler et al. (2001)–14 observed that no renal damage developed during the follow-up in 45 previously undamaged kidneys and progression of renal damage was rare (4 of 120 previously damaged kidneys), despite persisting reflux in half of the cases and episodes of acute pyelonephritis during follow-up. They concluded that congenital and/or hereditary factors could not be discarded as background factors for the development of renal damage.

Antibiotic prophylaxis

Medicines to treat Infections, high blood pressure and protein in the urine are usually given with surveillance to VUR patients, if the condition is not severe. Kohler et al. (2001)15 compared the long term effects in adults of conservative treatment and anti-reflux surgery for vesicoureteral reflux on urinary-tract infections, renal function, and loin pain. They gave conservative treatment to 46 patients (36 women) and anti-reflux surgery performed in 57 patients. The results showed that the frequency of acute pyelonephritis was significantly reduced after anti-reflux surgery ($P< 0.0001$), as well as after the diagnosis of vesicoureteral reflux in the group given conservative treatment. The frequency of lower-urinary-tract infections was not altered in either group.

Similarly, Neves et al. (1984) 16 managed medically for a mean of 87 months, a group of 27 adults with bilateral primary vesicoureteral reflux diagnosed during a 10-year interval. Their outcome was compared to that of 67 adults with bilateral primary reflux treated surgically during the same interval. The two groups appeared to fare equally well during the follow up of up to 13 years.

Similarly, a daily low dose of continuous antibiotic prophylaxis (CAP) is used in order to maintain sterile urine and prevent renal scarring occurring in the setting of febrile UTI. It may also offer more time for reflux to resolve spontaneously, avoiding the morbidity associated with surgical treatment 17. However, Keren et al. (2008) 18 demonstrated the lack of effectiveness of CAP to prevent pyelonephritis recurrences, renal scarring, and UTI, based on a randomized study in children. Similarly, Senoh et al. (1977) 19, after evaluating the value of conservative treatment for non-obstructive vesicoureteral reflux in 158 adult patients, observed that conservative, long-term chemotherapy eradicate the reflux in patients.

Surgical treatment

Surgical correction is resorted to patients who are unlikely to resolve VUR spontaneously and at higher risk for pyelonephritis and renal scarring. Patients who suffer from breakthrough UTIs despite the use of CAP are also identified for surgical corrections. Patients presenting with persistent high-grade reflux, particularly if bilateral, or new renal scars are also candidates for surgical treatment 15. Girls with persistent VUR after puberty are advised for corrective surgery, as reflux in adult females carries an increased propensity for maternal and fetal morbidity during pregnancy[20].

Endoscopic injection

Endoscopic treatment is a minimally invasive treatment, and the application of endoscopic injection therapy is gaining more acceptance with VUR treatment, as the techniques for and the bulking agents are continually improving. High-risk groups of VUR (grade IV) or previous treatment failures are now considered eligible for endoscopic management. The endoscopic injection of VUR creates reliable support behind the intravesical ureter without impeding the normal flow of urine from the kidneys to the bladder [17]. Endoscopic Vesicoureteral reflux management injection has been shown to be effective in adults with VUR. It remains an excellent surgical option for patients with VUR and breakthrough UTI after puberty 21. Endoscopic injection of VUR is now considered a first-line surgical treatment for low-grade reflux, although it may not be as effective as ureteral preimplantation, especially for high-grade VUR, and that long-term efficacy is still unknown[17].

Injection technique

Endoscopic injection is usually performed as day surgery under general anesthesia in a lithotomy position. Cystoscopy is performed, and the injection needle is placed through the operating channel of the cystoscope. The needle and syringe vary with the bulking subureteral agent and the manufacturer. The three most popular techniques described are the Teflon injection (STING), the hydrodistention technique (HIT), and the double hydrodistention technique (double-HIT) The STING technique consists of the injection of bulking agent, regardless of the agent, into the detrusor muscle immediately beneath the ureteral orifice at the six o'clock position. With the HIT, the ureter is distended with irrigation fluid from the cystoscope and the injection is made within the ureteral orifice, beneath the mucosa. The double-HIT is similar, but two injections are performed. The first injection is performed more proximally within the ureteral tunnel, and a second injection more distally, just under the ureteral orifice. Regardless of the technique used, it is recommended to avoid multiple punctures and to wait for 20 30 seconds with the needle in place after the injection to avoid agent leakage. After the surgery, patients can immediately return to their normal activities. Follow up usually includes an ultrasound to rule out de novo hydronephrosis/obstruction. A voiding cystourethrography is performed in select cases 17. A recent meta-analysis showed that the overall resolution of VUR was significantly higher for patients who underwent HIT (82.5%) compared to those who underwent STING (71.4%)17.

Bulking agents

Bulking agents are injectable substances used to increase tissue bulk and are used for endoscopic treatment of VUR. Several products have been developed, and the critical factors in determining the optimal product are biocompatibility, durability, and absence of migration. The first FDA-approved product was cross-linked collagen (e.g., Contigen®, Zyderm®, Zyplast®). However, Cross-linked bovine collagen was abandoned by most centres because of the shrinkage of the bulking agent and the reported immunological reactions after the injection of collagen. Other bulking agents include dextranomer/hyaluronic acid copolymer (Deflux®), carbon-coated beads (e.g., Durasphere®), spherical particles of calcium hydroxylapatite (CaHA) in a gel carrier (Coaptite®), and polydimethylsiloxane (Macroplastique®). Polydimethylsiloxane (PDMS, Macroplastique®) and dextranomer/ hyaluronic acid (Dx/HA, Deflux®) are two popular bulking agents. It was shown that polymethylmethacrylate/dextranomer injection could be used to treat vesicoureteral reflux with comparable efficacy to other substances currently used and a low rate of complications 22. PDMS has gained popularity in the treatment of VUR because of its low risk of migration due to its large particle size, composition, texture, and the absence of shrinkage. Many groups have compared the results obtained with a single injection of PDMS vs. Dx/HA copolymer for VUR endoscopic treatment. The results are variable, ranging from no difference to a better success rate with PDMS [23]. The other two agents used for endoscopic injection of VUR: polyacrylate-polyalcohol copolymer (PPC, Vantris®) and polyacrylamide hydrogel (PAHG, Bulkamid®). A multicentre survey showed a success rate of 93.8% after a single injection of PPC. However, concerns have been raised with PPC regarding a high rate of ureteral obstruction[17].

Complications associated with endoscopic injection treatment in

adults are low. Mild hematuria can occur following injection. When it happens intraoperatively, it is recommended to empty the bladder and to gently apply the tip of the cystoscope at the bleeding site until the bleeding stops. UTI may also occur [17]. Lorezo (2016) 24 reported de novo contralateral VUR after the surgery, but the rate was very low to a level of 4.5 -7%. However, concerns were raised about long-term efficacy and complications associated with endoscopic injection 25. The implanted agent could become calcified, leading to hematuria, intermittent back pain, necrosis of the bladder mucosa, erosion of the bulking agent, and wrong diagnosis of distal ureteral lithiasis.

Ureteral reimplantation (Ureteroneocystostomy)

The original ureter is surgically re-positioned (reimplanted) in the bladder wall. Different surgical approaches are used, and the best one depends on the patient's condition and the surgeon's experience and preferences. Regardless of the type of procedure, many surgical principles may be followed to obtain a reasonable success rate. Successful surgery includes creation of a sealed tension-free ureteral anastomosis, preservation of the delicate blood supply to the distal ureter, creation of a submucosal tunnel length five times longer than the diameter of the ureter over a firm backing, delicate handling of the bladder, and an adequate anastomosis preventing stenosis, twisting, and wrong angulation of the ureter [17]. The gold standard is an open surgery, but transperitoneal laparoscopic extravesical and intravesical ureteral reimplantations are also common. Laparoscopic extravesical techniques seem to be beneficial in the adolescent and adult populations. Robot-assisted laparoscopic ureteral reimplantation (extra and intravesical) is also receiving acceptance now. Dirie and Wang (2020) [26] performed robot-assisted ureteroneocystostomy (RAUN) in 30 adult patients from 2015 to 2018 and reported no intraoperative complications. However, a wide range of success rates, and many variations in the surgical technique are reported[17].

Complications connected with ureteral reimplantation include UTI, hematuria, contralateral VUR, and obstruction. Nevertheless, the estimated rate of occurrence is 1%27.

Vesicoureteral reflux in the kidney graft

Vesicoureteral reflux (VUR) is one of the most common ureteric complications after kidney transplantation that might cause symptomatic infections which deteriorate graft function. Surgical reimplantation has been the standard treatment, but recently, endoscopic injection is an alternative approach. VUR in the transplanted kidney is related to delayed graft failure. Gutiérrez-Jiménez et al. (2019) 28 reported the results of polydimethylsiloxane application in the endourological management of symptomatic vesicoureteral reflux to the kidney graft of 23 patients, which showed that 18 (78.3%) patients presented clinical success. Similarly, Wang et al. (2019) 29 reported 75% of clinical success with kidney graft patients of systemic VUR performed with Endoscopic Deflux injections.

5. Conclusion

VUR is a complex physiological disorder that is not fully understood. It requires further studies in all branches of the medical field. Available literature shows that the present treatment of antibiotic prophylaxis, endoscopic injection of a bulking agent, and ureteral reimplantation are options of treatment with varying levels of satisfaction. However, all studies underline the role of gene markers associated with VUR. Hence, more work on genetic engineering is required to find out a viable solution for UVR and associated issues.

6. REFERENCES

1. Routh JC, Bogaert GA, Kaefer M, et al. Vesicoureteral reflux: current trends in diagnosis, screening, and treatment. European urology 2012; 61(4): 773-82.
2. Dave S, Khoury AE. The current evidence based medical management of vesicoureteral reflux: The Sickkids protocol. Indian journal of urology : IJU : journal of the Urological Society of India 2007; 23(4): 403-13.
3. Nayak S, Sharma N, Jindal A. Urinary tract infection and vesicoureteric reflux. Journal of Integrative Nephrology and Andrology 2017; 4(2): 39-46.
4. Rollino C, D'Urso L, Beltrame G, Ferro M, Quattrocchio G, Quarello F. [Vesicoureteral reflux in adults]. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia 2011; 28(6): 599-611.
5. Meena J, Hari P. Vesicoureteral reflux and recurrent urinary tract infections. Asian Journal of Pediatric Nephrology 2019; 2(2): 61-70.
6. Sakhuja V, Muthukumar T, Sud K, et al. Vesicoureteric Reflux and Reflux Nephropathy as Seen at a Tertiary Care Adult Nephrology Service in India—An Analysis of 86 Patients. Renal Failure 2003; 25(2): 173-81.
7. Kamil ES. Recent advances in the understanding and management of primary vesicoureteral reflux and reflux nephropathy. Current opinion in nephrology and hypertension 2000; 9(2): 139-42.
8. Mattoo TK. Vesicoureteral reflux and reflux nephropathy. Adv Chronic Kidney Dis 2011; 18(5): 348-54.
9. Cornwell LB, Riddell JV, Mason MD. New-Onset ESRD Secondary to Reflux Nephropathy has Decreased in Incidence in the United States. Journal of Pediatric Urology 2020.
10. Pereira B, Macedo C, Anacleto S, Gonçalves M, Lima E, Carvalho-Dias E. Late presentation of vesicoureteral reflux: An unusual cause of pyelonephritis in adults. Int J Surg Case Rep 2018; 53: 238-41.
11. Nelson CP, Koo HP. Pediatric Vesicoureteral Reflux. Available online: https://emedicine.medscape.com/article/1016439-overview (accessed on 11 July 2020. Medscape; 2020.
12. Carlos Roberto Estrada J, Cendron M. Vesicoureteral Reflux Treatment & Management. Available online: https://emedicine.medscape.com/article/439403-treatment. accessed on 11 July 2020. Medscape 2018
13. Nelson CP, Koo HP. Pediatric Vesicoureteral Reflux Treatment & Management. Available online: https://emedicine.medscape.com/article/1016439-treatment (accessed on 17 July 2020). Medscape 2018
14. Köhler J, Thysell H, Tencer J, Forsberg L, Hellström M. Long-term follow-up of reflux nephropathy in adults with vesicoureteral reflux – radiological and pathoanatomical analysis. Acta Radiologica 2001; 42(4): 355-64.
15. Köhler J, Thysell H, Tencer J, Forsberg L, Hellström M. Conservative treatment and anti-reflux surgery in adults with vesico-ureteral reflux: effect on urinary-tract infections, renal function and loin pain in a long-term follow-up study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2001; 16(1): 52-60.
16. Neves RJ, Torres VE, Malek RS, Svensson J. Vesicoureteral reflux in the adult. IV. Medical versus surgical management. J Urol 1984; 132(5): 882-5.
17. Blais A-S, Bolduc S, Moore K. Vesicoureteral reflux: From prophylaxis to surgery. Can Urol Assoc J 2017; 11(1-2Suppl1): S13-S8.
18. Keren R, Carpenter M, Greenfield S, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 2008; 122(6): 1409-10; author reply 10-1.
19. Senoh K, Iwatsubo E, Momose S, Goto M, Kodama H. Non-Obstructive Vesicoureteral Reflux in Adults: Value of Conservative Treatment. The Journal of Urology 1977; 117(5): 566-70.
20. Hollowell JG. Outcome of pregnancy in women with a history of vesico-ureteric reflux. BJU international 2008; 102(7): 780-4.
21. Moore K, Bolduc S. Treatment of Vesicoureteral Reflux in Adults by Endoscopic Injection. Urology 2011; 77(6): 1284-7.
22. Kim SW, Lee YS, Im YJ, Han SW. New bulking agent for the treatment of vesicoureteral reflux: Polymethylmethacrylate/dextranomer. Investig Clin Urol 2018; 59(3): 206-12.
23. Moore K, Bolduc S. Prospective Study of Polydimethylsiloxane vs Dextranomer/Hyaluronic Acid Injection for Treatment of Vesicoureteral Reflux. Journal of Urology 2014; 192(6): 1794-800.
24. Lorenzo AJ, Khoury AE. Endoscopic treatment of reflux: management pros and cons. Current opinion in urology 2006; 16(4): 299-304.
25. Kim SW, Lee YS, Han SW. Endoscopic injection therapy. Investig Clin Urol 2017; 58(Suppl 1): S38-S45.
26. Dirie NI, Wang S. Robot-assisted laparoscopic ureteroneocystostomy in adults: A single surgeon experience and literature review. Asian Journal of Urology 2020; 7(1): 37-44.
27. Steffens J, Langen PH, Haben B, Hiebl R, Steffens L, Polsky MS. Politano-leadbetter ureteroneocystostomy. A 30-year experience. Urologia internationalis 2000; 65 1: 9-14.
28. Gutiérrez-Jiménez AA, Jiménez-López LA, Ricardez-Espinosa AA, et al. Aplicación endourológica de polidimetilsiloxano en pacientes con reflujo vesicoureteral sintomático en injerto renal. Actas Urológicas Españolas 2019; 43(5): 262-8.
29. Wang HH, Ding WF, Chu SH, et al. Endoscopic Treatment for Post-Transplant Vesicoureteral Reflux. Transplantation proceedings 2019; 51(5): 1420-3.