



Implementation of Novel Fetal Intervention for Fetal Lower Urinary Tract Obstruction and the Importance of Candidate Selection: A Case Report

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Fetal lower urinary tract obstruction (LUTO) is a congenital condition in which the bladder fails to excrete urine through the urethra. The primary goal of prenatal treatment for LUTO is the prevention of renal impairment and pulmonary hypoplasia. Vesico-amniotic shunt (VAS) has been the fetal intervention of choice; however, VAS has some limitations, including excretion of urine through an unphysiologic bypass and the need for postnatal corrective reoperation. In this study, we present a novel fetal intervention, a “retro-cystoscopic urethral approach,” performed on a male fetus at 20 weeks gestation diagnosed with enlarged bladder and bilateral hydronephrosis. This approach aims to dilate the narrowed urethra by inserting a urinary catheter using guidewire through a fetal cystoscope. The whole procedure was monitored under real-time ultrasonographic guidance. Despite prenatal intervention, the fetus required multiple cystocenteses, and the bladder dilation persisted. Postnatally, he was diagnosed with megacystis microcolon intestinal hypoperistalsis syndrome, a non-obstructive condition which is relatively rare in male infants. Our case emphasizes the complexity of diagnosing LUTO during the prenatal period. Further studies exploring novel prenatal interventions should pay more attention to candidate selection. Additionally, a thorough evaluation of organ systems beyond the urinary tract is necessary.

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Introduction

Fetal lower urinary tract obstruction (LUTO) causes progressive upper urinary tract changes, including hydronephrosis and destruction and degeneration of renal parenchyma, which cause varying degrees of renal dysfunction after birth and end-stage renal disease that occurs early in infancy. Fetal LUTO also causes oligohydramnios or anhydramnios, leading to secondary pulmonary hypoplasia and various perinatal complications, including fetal death.¹ Therefore, LUTO treatment aims to prevent the pregression of renal impairment and pulmonary hypoplasia. Currently, the primary approach to prenatal intervention is the vesico-amniotic shunt (VAS).² However, this method of bypassing the narrowed urethra to divert urine into the amniotic cavity does not eliminate the underlying cause of urethral obstruction during the prenatal period.

During fetal development, the bladder detrusor muscle forms around 9 to 12 weeks of gestation, but the hypertrophy of circular muscle and functional maturation of the bladder continue until the end of gestation. Therefore, restoring urinary outflow through the bladder outlet during the prenatal period may promote the functional development of the fetal bladder. Also, VAS requires additional postnatal corrective surgery to resolve the urethral obstruction.

In this study, we devised a novel prenatal intervention to perform corrective urethral dilation prenatally by inserting a urethral catheter into the posterior urethral opening using fetal cystoscopy. Herein, we report the case of a male infant diagnosed with LUTO prenatally, who was successfully operated with this procedure on 20 weeks of gestation, but was diagnosed with megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) postnatally. This study was reviewed and approved by the Institutional Review Board (IRB) of Chung-Ang University Hospital (IRB No. 2022-012-19406).

Case

A 31-year-old multipara with an obstetrical history of 1-0-0-1 was referred for suspected fetal LUTO in the mid-trimester. The mother and husband were Korean and had no specific past or family medical history. At the time of the visit, the mother was 15 weeks and 6 days of gestation, and the fetal abdominal circumference, biparietal diameter and head circumference were adequate for a 16-week gestation. Three consecutive fetal cystocentesis performed between 16 to 18 weeks of gestation for urinary biochemical examination revealed that the prognosis of fetal renal function was

favorable (Table 1).³ The karyotype was normal at 46 XY, and no numerical abnormalities were observed in chromosome analysis performed via amniocentesis. After cystocentesis, follow-up ultrasonography at 18 weeks gestation revealed a bladder diameter of 39 mm, consistent with megacystis. At 19 weeks gestation, increased partial echogenicity was noted in the fetal renal parenchyma. At 20 weeks and 6 days gestation, the fetal prognosis, including the risks of pulmonary hypoplasia and progressive renal parenchymal damage, was explained during family counseling. The obstetrician explained a novel surgical method, the “fetal retrocystoscopic urethra approach” to mother and obtained written consent for the surgery.

The mother was placed in supine position and the abdomen was sterilized after general anesthesia. Under ultrasound guidance, the trocar was passed through the mother’s abdomen, through the uterus, and into the fetal bladder. A 3-mm diameter fetal endoscope was entered into the fetal bladder through the trocar, and a guidewire was passed through the fetal endoscope into the posterior urethral orifice of the fetus (Fig. 1A, B) and positioned outside the external urethral orifice. A 3-french size urethral catheter was advanced through the guidewire from the fetal bladder toward the external urethral orifice, and real-time ultrasonography confirmed that the distal end of the catheter had exited into the amniotic cavity space (Fig. 1C). The catheter was secured from the fetal bladder through the uterus to the skin of the mother’s abdomen for 24 hours functioning as a urethral stent and was removed percutaneously.

However, a follow-up ultrasound performed at 22 weeks of gestation showed that fetal bladder was still dilated. The mother was subsequently hospitalized for multiple cystocen-

Table 1. Fetal Cystocentesis Results Performed between 16 to 18 Weeks of Gestation

Analyte	First (16 wk and 0 day pregnant)	Second (16 wk and 2 day pregnant)	Third (17 wk and 0 day pregnant)	Good prognosis	Poor prognosis
Sodium (mmol/L)	83	76	91	<90	>100
Chloride (mmol/L)	72	67	78	<80	>90
Calcium (mg/dL)	4.3	4.2	5.0	<7	>8
Osmolarity (mOsm/L)	182	159	198	<180	>200
β-2-microglobulin (mg/L)	2.96	3.16	5.9	<6	>10
Total protein (mg/dL)	4.6	2.5	16.2	<20	>40

Cystocentesis results indicate a favorable prognosis. Based on ref. 3.

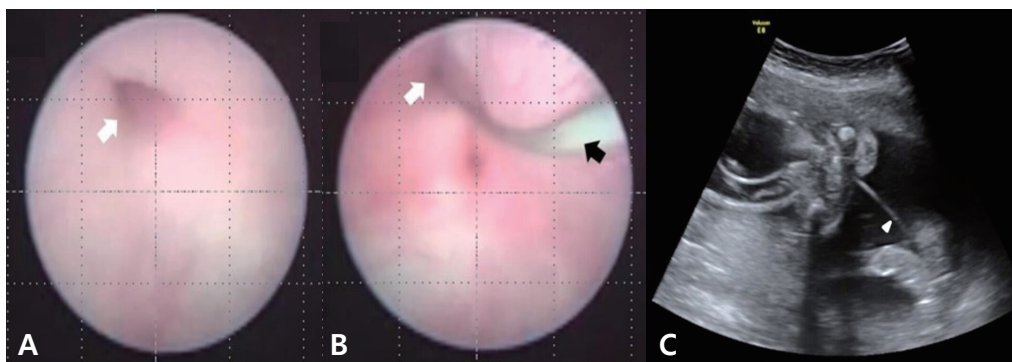


Fig. 1. (A) The entry to the posterior urethral orifice can be seen as indicated by the white arrow. (B) The urethral catheter, indicated by the black arrow, is entered through the posterior urethral orifice. (C) The distal part of the urethral catheter, indicated by the white arrowhead, is protruding into the amniotic cavity. The patients' parents provided written informed consent for the publication and use of their child's images.

testes and amnioinfusion. When she was hospitalized at 30 weeks and 4 days gestation, uterine contraction occurred; thus, a cesarean section was decided to perform at 32 weeks of gestation, considering the degree of fetal lung development.

At 32 weeks of gestation, a boy weighing 1,690 grams was delivered via cesarean section with an Apgar scores of 8 at 1-minute and 10 at 5-minute. A small bowel hernia was noted in the right abdomen was, but the umbilical cord appeared normal and no hernia sac was observed. On the day of birth, a corrective surgery for the small bowel hernia was performed along with a cystoscopy. No posterior urethral valve was identified at the verumontanum of the prostatic urethra. After confirming the absence of urethral stricture or obstruction, the procedure was completed with the placement of an indwelling urethral catheter. He had no meconium passage until 12 days after birth. A gastrografen enema was performed, which confirmed the findings of a microcolon (Fig. 2). Diagnostic laparotomy performed and a biopsy from the terminal ileum showed reduced expression of smooth muscle actin in immunostain (Fig. 3). The patient was diagnosed with MMIHS and transferred to another hospital for prolonged total parenteral nutrition and the possibility of bowel transplantation.

Discussion

LUTO—a heterogeneous group of various congenital ano-



Fig. 2. The gastrografen enema shows the finding of a microcolon. The patients' parents provided written informed consent for the publication and use of their child's images.

malies that primarily cause narrowing of the fetal bladder neck—reportedly accounts for approximately one-third of fetal kidney anomalies detected at autopsy after termination of pregnancy and is identified in 3.34 newborns per 10,000 surviving infants.⁴ The most common causes of LUTO are posterior urethral valve and urethral atresia or stricture.

Surviving infants of LUTO develop varying degrees of renal impairment, with a lifetime incidence of end-stage renal disease as high as 30%.⁵ Therefore, early diagnosis of LUTO

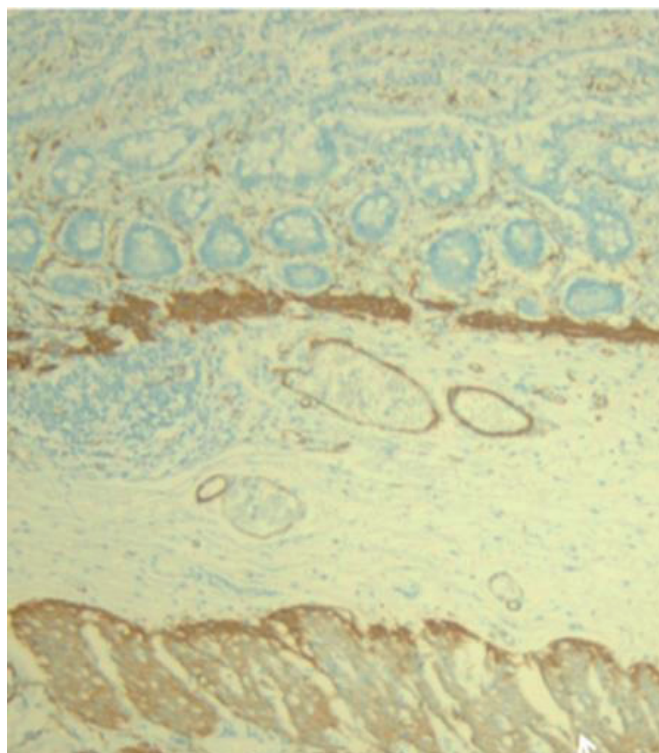


Fig. 3. Reduced alpha-smooth muscle actin immunoreactivity in terminal ileum can be seen as indicated by the white arrow (immunostain, $\times 100$). The patients' parents provided written informed consent for the publication and use of their child's images.

and prediction of postnatal renal function are important for candidate selection for prenatal intervention. Currently, LUTO diagnosis is established via prenatal ultrasound, and the typical ultrasound findings are bladder distension, unilateral or bilateral hydronephrosis, and oligohydramnios.⁶ Prediction of postnatal renal function is traditionally assessed by performing 3 cystocenteses to measure the sodium concentration, calcium concentration, osmolarity, total protein, and beta 2-microglobulin concentration of fetal urine.⁷ Categorizing LUTO severity is essential for selecting candidates for fetal intervention; however, no uniform criteria currently exist. In 2022, the European Reference Network for Rare Kidney Diseases proposed a clinical recommendation which categorized the severity into 3 levels based on ultrasound findings, amniotic fluid index, and prenatal urine test results. Moderate stage was defined as the presence of a decreased amniotic fluid index and increased echogenicity of the renal cortex but with a predicted favorable prognosis on fetal urinalysis and no renal cortical cysts or renal dysplasia.

Clinical recommendation suggests that prenatal intervention at the moderate stage can provide benefits for improving pulmonary and renal outcomes.³

The current mainstay of prenatal intervention is VAS, in which a bypass is placed between the fetal bladder and amniotic cavity to reduce intra-bladder pressure and drain urine into the amniotic cavity. This bypass prevents oligohydramnios and pulmonary hypoplasia as it allows urine to drain from fetal bladder into amniotic cavity. Previous literature confirmed an increased perinatal survival rate especially up to 6 months after birth.³ However, it has been reported that VAS carries a risk of procedure-related complications in up to 40% of cases, such as shunt dislocation, fetal ascites, preterm labor, and occasionally fetal death. Furthermore, meta-analysis revealed no significant difference of long-term kidney function and survival rate at 2 years after birth compared to conservative treatment.⁸ In addition, VAS does not affect the restoration of physiological urine excretion from the bladder through the urethra as it excretes urine through a bypass and has the limitation of requiring corrective surgery after birth. Thus, several researches are being conducted on novel surgical methods to remove the cause of urethral obstruction radically in uterus. Debska et al.⁹ reported a case series of patients with posterior urethral valve syndrome in whom urethral balloon dilatation using a percutaneous coronary angioplasty catheter was successful in restoring fetal self-voiding function.

In this study, the authors attempted a "retrograde urethral approach through the fetal cystoscope," which involves accessing the prostatic urethra through the fetal cystoscope, passing a urethral catheter and exiting it through the external urethral orifice, leaving the catheter in place for one day to dilate urethra, and then removing it. To the best of our knowledge, this surgery was totally novel approach and the firstly performed by the authors. It is designed for posterior urethral valve and urethral stricture, which are the most common causes of LUTO. Compared to conventional VAS, it has the advantage of directly resolving urethral obstruction in a more physiological way, helping to restore the bladder's natural urinary excretion function. Compared to another conventional fetal intervention, cystoscopic laser ablation, this new approach can also be applied to strictures within the

urethra, as it allows a guidewire to pass through narrowed portion and enables direct dilation of the stricture with a stent. Additionally, compared to Debska et al's method,⁹ this approach is more cost-effective as it uses inexpensive, easily accessible urethral catheters.

However, although the patient met the criteria for prenatal intervention under the existing severity classification, he was diagnosed with MMIHS postnatally. MMIHS is primarily caused by mutations in the *ACTG2* gene and is characterized by a dilated non-obstructive bladder, small colon, and intestinal hypoperistalsis caused by abnormalities in actin filament and smooth muscle function in the small intestine and bladder.¹⁰ It occurs more frequently in girls and is difficult to differentiate from fetal LUTO because of the similar findings of a megabladder and bilateral hydronephrosis on prenatal ultrasound. However, it is a non-obstructive condition with congenital inability of the bladder to self-void, and prenatal interventions other than VAS are not effective for this condition. Therefore, our new method needs to be reassessed in patients who meet the original indications, such as posterior urethral valve or urethral stricture. In this case, bladder dilatation recurred after the prenatal intervention; thus, repeated cystocentesis were performed, and an incisional hernia occurred at the surgical region.

Reports indicate that up to one-third of cases suspected of LUTO on prenatal ultrasound were diagnosed with non-obstructive causes postnatally. Therefore, further research is needed to refine the current differential diagnosis of LUTO and the criteria for selecting candidates for prenatal interventions. Researchers should consider the possibility of conditions beyond posterior urethral valves or urethral stricture, which are the primary indications for prenatal intervention. A thorough evaluation of organ systems outside the urinary tract is necessary, and, if needed, imaging studies such as fetal MRI may be helpful.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Authors' Contributions

Conceptualization: all authors; Investigation: GJK; Project administration: GJK; Resources: SH; Supervision: NML, GJK; Validation: GJK; Visualization: SYA, NLY; Writing-original draft preparation: WSC; Writing-review & editing: all authors.

References

- 1) Farrugia MK. Fetal bladder outlet obstruction: embryopathology, in utero intervention and outcome. *J Pediatr Urol* 2016;12:296-303.
- 2) Clayton DB, Brock JW. Current state of fetal intervention for lower urinary tract obstruction. *Curr Urol Rep* 2018;19:12.
- 3) Capone V, Persico N, Berrettini A, Decramer S, De Marco EA, De Palma D, et al. Definition, diagnosis and management of fetal lower urinary tract obstruction: consensus of the ERKNet CAKUT-obstructive uropathy work group. *Nat Rev Urol* 2022;19:295-303.
- 4) Malin G, Tonks AM, Morris RK, Gardosi J, Kilby MD. Congenital lower urinary tract obstruction: a population-based epidemiological study. *BJOG* 2012;119:1455-64.
- 5) Heikkila J, Holmberg C, Kyllonen L, Rintala R, Taskinen S. Long-term risk of end stage renal disease in patients with posterior urethral valves. *J Urol* 2011;186:2392-6.
- 6) Fontanella F, Duin LK, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, et al. Prenatal diagnosis of LUTO: improving diagnostic

- accuracy. *Ultrasound Obstet Gynecol* 2018;52:739-43.
- 7) Mann S, Johnson MP, Wilson RD. Fetal thoracic and bladder shunts. *Semin Fetal Neonatal Med* 2010;15:28-33.
- 8) Nassr AA, Shazly SA, Abdelmagied AM, Araujo Junior E, Tonni G, Kilby MD, et al. Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017;49:696-703.
- 9) Debska M, Kolesnik A, Kretowicz P, Oledzka A, Rebizant B, Gastol P, et al. Urethroplasty with balloon catheterization in fetal lower urinary tract obstruction: observational study of 10 fetuses. *Ultrasound Obstet Gynecol* 2020;56:916-20.
- 10) Nakamura H, O'Donnell AM, Puri P. Consanguinity and its relevance for the incidence of megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS): systematic review. *Pediatr Surg Int* 2019;35:175-80.