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FETAL PROCEDURES

Two Cases of Fetal Lower Urinary Tract Obstruction (LUTO) with Similar Presentations Before But Contrasting Outcomes After Fetoscopic Laser Fulguration of Posterior Urethral Valves

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Abstract Posterior urethral valves (PUV) are the commonest cause of lower urinary tract obstruction detected during the antenatal and immediate postnatal period in male fetuses. Treatment options for PUV during the antenatal period include percutaneous vesico-amniotic shunt, fetoscopic fulguration of the valve and open fetal cystostomy. We report two cases of fetal cystoscopic laser valvotomy with fairly similar pre-operative profiles but contrasting postnatal outcomes, which re-iterates the fact that case selection in such cases continues to be a challenge. These are the first case reports on fetoscopic laser valvotomy in India to the best of our knowledge.

Keywords Lower urinary tract obstruction · LUTO · Posterior urethral valves · Laser ablation · Fetal cystoscopy

Introduction

Posterior urethral valves (PUV) are the commonest cause of lower urinary tract obstruction (LUTO) detected during the antenatal and immediate postnatal period in male fetuses [1], with a reported incidence of 1 in 5,000 live births. They account for at least 70–80% of all causes of LUTO, the rest being made up by urethral atresia or stenosis [2, 3]. Prenatally diagnosed cases of PUV, particularly if associated with severe oligohydramnios before 24 weeks of gestation, have a high mortality rate of over 90%, primarily due to pulmonary hypoplasia. Even with survivors, the postnatal course is complicated by progression from renal cortical damage to end-stage renal failure requiring dialysis and/or transplantation [4, 5].

Treatment options for PUV during the antenatal period include percutaneous vesico-amniotic shunt, fetoscopic fulguration of the valve and open fetal cystostomy. Vesico-amniotic shunt and open fetal cystostomy have their own limitations. The shunt can get obstructed and displaced in 19% cases [6] requiring re-interventions. Open fetal cystostomy requires maternal laparotomy and hysterotomy and has high maternal morbidity. Fetal endoscopic fulguration of posterior urethral valves is, however, comparatively less invasive as it requires only a 2–3 mm incision on the maternal abdomen and may obviate the need for repeated interventions during the pregnancy, thereby decreasing maternal and/or fetal complications [7]. It is widely regarded as the procedure of choice in the antenatal treatment of PUV.

However, case selection is often difficult and none of the antenatal urinary parameters of renal function are sufficiently accurate to predict postnatal renal function [8]. We report two cases of fetal cystoscopic laser valvotomy with fairly similar pre-operative profiles but contrasting postnatal outcomes, which re-iterates the fact that case selection in such cases continues to be a challenge. These are the first case reports on fetoscopic laser valvotomy in India to the best of our knowledge.

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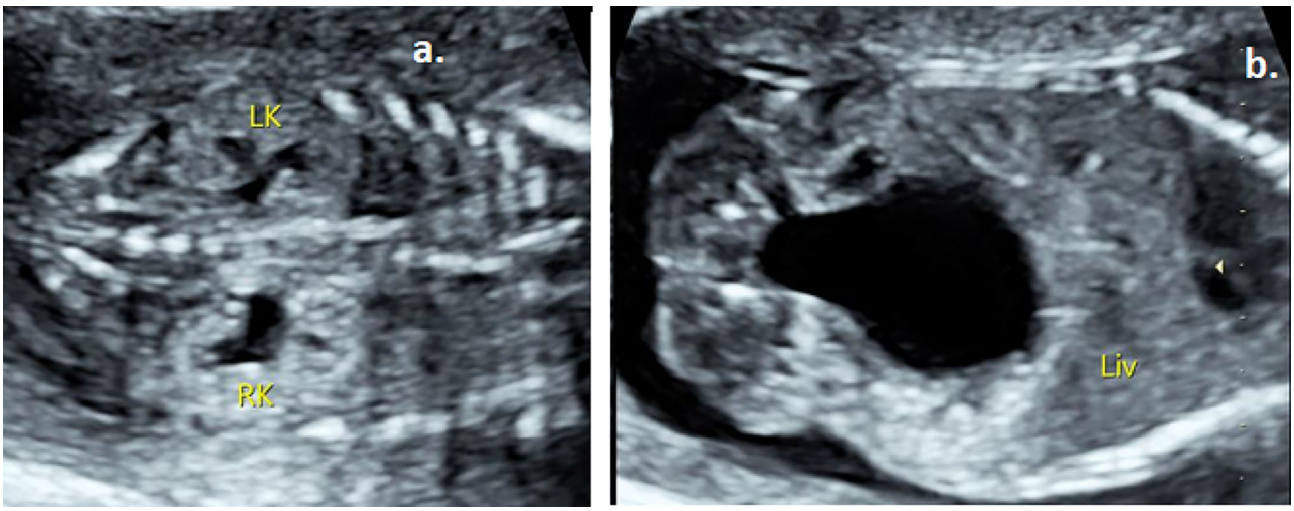

Fig. 1 Ultrasound images before fetal surgery: demonstration of "Echogenic kidneys" (**a**) distended bladder with typical "key-hole" sign (**b**)

Case 1

A 32-year-old second gravida in a non-consanguineous marriage, with a prior ectopic pregnancy presented to us at 17 weeks and 1 day of gestation for a second opinion on megacystis. Her first trimester scan was unremarkable and a scan done at the referring hospital at 17 weeks showed features suggestive of bladder outlet obstruction—distended bladder, dilated proximal urethra (keyhole sign) and oligohydramnios (Deepest Vertical Pool of 1 cm). She was referred for a second opinion and possible fetal intervention. These scan findings were confirmed and it was noted that the fetus was male. The deepest vertical pocket (DVP) of amniotic fluid was 2.7 cm. Both fetal kidneys were hyperechoic at presentation but the cortico-medullary differentiation was reasonably preserved. She was followed up weekly for reassessment of the kidneys, urinary bladder and amniotic fluid. At 18 weeks 4 days, a falling trend in amniotic fluid (DVP of 2.1 cm) and progression of the severity of the bladder obstruction was noted. A week later, there was further deterioration—the option of a vesicocentesis for urine osmolality and electrolytes was offered and accepted. The third fetal urine sample (after sending the first for FISH and karyotyping and discarding the second sample, on two successive days) showed a sodium of 84 mmol/L, chloride of 54 mmol/L; Calcium of 4.26 mg/dl and osmolality of 168 mOsm/K, suggesting preserved renal function [9]. Beta-2 microglobulin was not assessed as the test was not available in-house and outsourced samples would return results only in 10 days. The family was therefore given the option of therapeutic fetal intervention by fetal cystoscopy and laser fulguration and the pros and cons of the procedure were discussed in detail. They opted for the same and surgery was performed at 20 weeks 2 days gestation under local anesthesia.

Post procedure, a deepest vertical pocket of 3.2 cm was demonstrated which improved to 4.4 cm on post procedure day 3. The couple, who were foreign residents, went back to their resident country and were advised weekly scans for serial assessment of amniotic fluid and kidneys. Weekly scans for the next five weeks showed normal amniotic fluid volumes. The scan in her 6th post operative week, however, showed a sudden fall in amniotic fluid volume. She came back to us at 26 weeks 5 days and a review scan showed bilateral small echogenic kidneys, hydroureter, normal sized bladder and anhydramnios suggesting bilateral renal failure. The family were counseled regarding the poor prognosis. The case was discussed at the fetal board and the options of continuation of pregnancy till term versus preterm induction of labour were given to the couple. They opted for the latter. A therapeutic amnioinfusion was done to facilitate vaginal delivery and she delivered a stillborn male fetus the next day. The parents opted out of a fetal autopsy. The karyotype was normal (Figs. 1, 2, 3).

Case 2

A 31-year-old third gravida from a non-consanguineous marriage presented at 19 weeks 3 days of gestation, with similar features of fetal LUTO, for a second opinion. She had two living children with the last childbirth 5 years ago. Her elder son had a history of posterior urethral valve which was treated postnatally and the child is doing fine. Her first trimester ultrasound scan in this pregnancy was normal. The anomaly scan done at 19 weeks and 3 days showed similar findings as in the first case. The deepest vertical pocket of amniotic fluid was 3 cm. A week later the amniotic fluid pocket fell to 2 cm. Following counseling, this family too opted for vesicocentesis. Sampling was performed for three days beginning at 21 weeks and

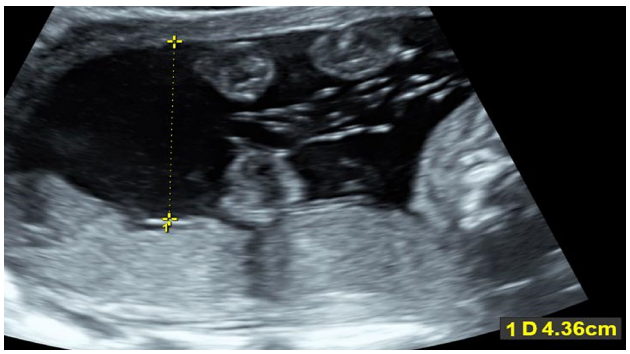

Fig. 2 Ultrasound images after fetal surgery: normal amniotic fluid at post procedure day 3

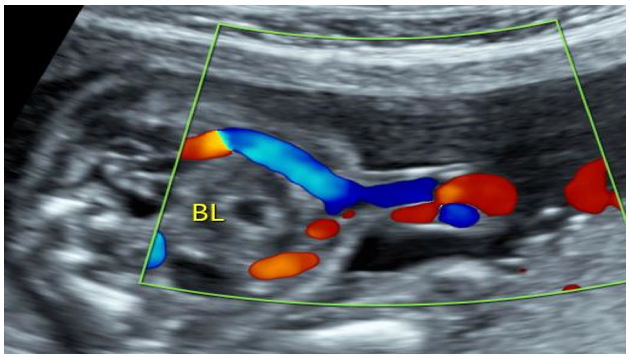

Fig. 3 Ultrasound images after fetal surgery: the shrunken bladder at post procedure day 3

2 days gestation. The first sample was sent for FISH and karyotyping, the results of which were normal. The third sample, on analysis, revealed sodium of 112 mmol/L, chloride of 82 mmol/L, calcium 9.34 mg/dl and osmolality of 211 mOsm/K, suggesting near favorable renal function. The same options of fetal intervention were discussed. This family too opted for fetoscopic laser ablation and the same was performed at 22 weeks and 2 days gestation. A scan on post procedure day 5 showed a amniotic fluid pocket of 3.4 cm and resolution of ultrasound findings of lower urinary tract obstruction. She was followed up weekly for an assessment of amniotic fluid and the urinary system. At 27 weeks of gestation, a follow up scan showed a "keyhole" bladder and bilateral hydroureteronephrosis suggesting reappearance of LUTO. The single deepest pocket of amniotic fluid was 4.2 cm. The option of a vesico-amniotic shunt was discussed with the couple but the same was declined. She was followed up weekly for amniotic fluid which showed a falling trend. At 30 weeks, elective LSCS was performed in view of near anhydramnios and a live male child of 1.7 kg was born. Serum creatinine at birth was 1.45 mg/dl.

However, it worsened to 3.7 mg/dl after 1 week and a cystoscopic fulguration of the PUV with bilateral ureterostomy was performed the same day. Kidney function improved 1 week after the procedure (S. creatinine of 1.31 mg/dl). At 6 months, the infant is doing well, maintaining reasonably good renal function. Ureterostomy was closed on one side with reimplantation of the ureter. The contralateral ureterostomy was not closed, to act as a vent and avoid high pressure in the urinary bladder (Figs. 4, 5, 6).

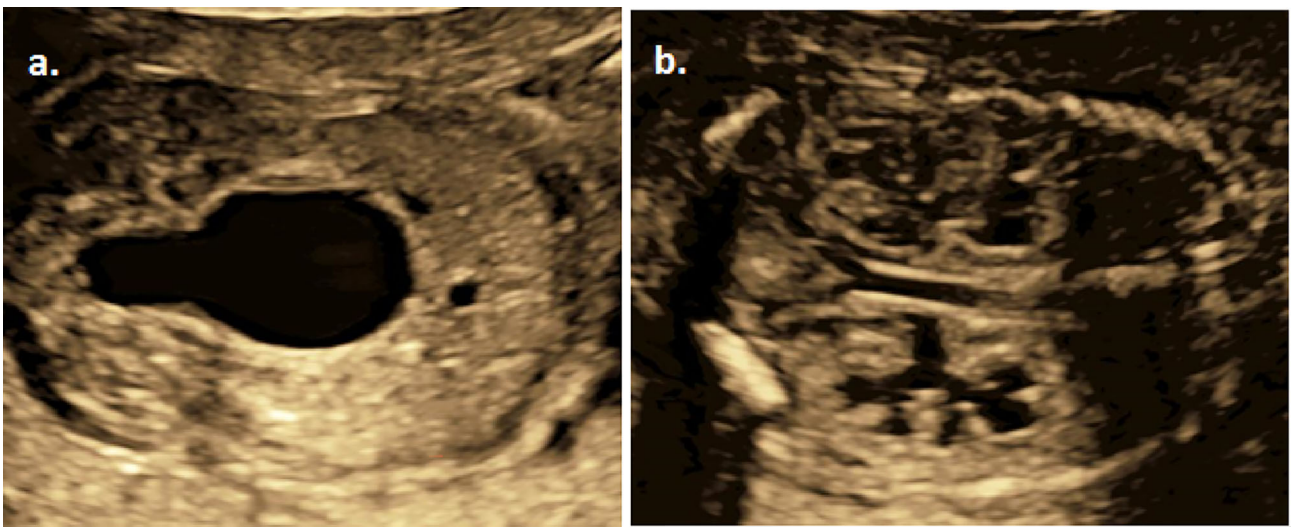

Fig. 4 Ultrasound images before fetal surgery showing the typical "keyhole" bladder at 19 weeks 3 days gestation (**a**) and bilateral pelvicalyceal dilatation with hyperechoic renal cortex (**b**)

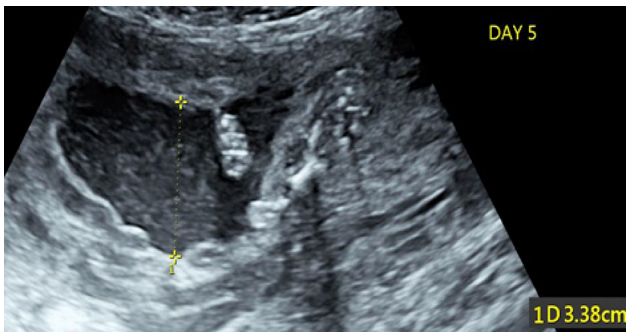

Fig. 5 Ultrasound images after fetal surgery; normal amniotic fluid volume at post procedure day 5

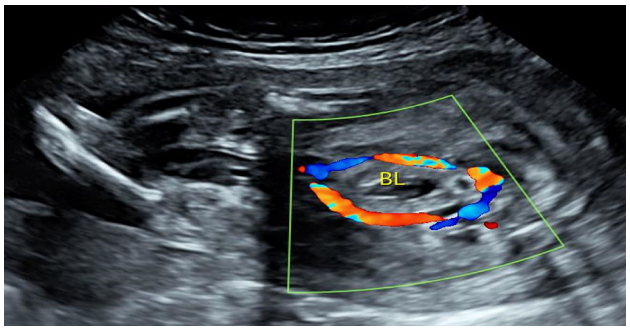

Fig. 6 Ultrasound images after the fetal surgery; post procedure day 5 showing shrunken bladder

Discussion

Lower urinary tract obstruction due to posterior urethral valves (PUV) is the most common cause of postnatal renal failure in male neonates [2]. Though fetoscopic PUV fulguration is well reported in western literature as the procedure of choice in fetal LUTO due to PUVs [10—22] this is still in its infancy in India. Our first-hand experience with these two cases tells us that fetoscopic laser valvotomy is a technically feasible option in most cases of lower urinary tract obstruction due to posterior urethral valves (PUV) in the Indian scenario as well.

Technique

Fetal cystoscopic fulguration was performed percutaneously under local anesthesia and ultrasound guidance. Since there was severe oligohydramnios and the fetal lie was favorable, fetal paralysis was not required. Fetal analgesia was achieved with Fentanyl 2 mcg/kg. A small 1.3 mm curved fetoscope was inserted through using a direct entry approach through both maternal and fetal anterior abdominal walls to enter the fetal urinary bladder through its anterior wall, closer to the dome, making sure that the curvature of the scope was aligned with the vesicourethral angle. Once inside the urinary bladder, a diagnostic cystoscopy was initially carried out to visually assess the bladder, the bladder neck and the fetal posterior urethra. PUV was identified in both cases as a slit-like whitish membrane obstructing the urethra, using the verumontanum as a guide. (In contrast, if a non-membrane like obstruction is found, even with fluid injection, it is most likely to represent urethral atresia and no attempt should be made to perforate this structure with laser; 20–30% of LUTO diagnosed in the second trimester and upto 50% diagnosed in the first trimester could be due to urethral atresia). On locating the PUV, the valve was ablated using a Dornier Medilabs Diode laser in standard mode delivered through a 400 nm laser fibre and the power set to 35 watts. Laser was applied with the fiber tip in contact with the PUV, till ablation of the PUV was achieved as evidenced by the appearance of a few bubbles that come up into the bladder from the posterior urethra. This may require one or more shots of laser. In both our cases, three to four shots were required. Minimal bladder decompression with peritoneal leak was observed in the second case intra-operatively, but this did not interfere with completion of the procedure. No fluid infusion was required as the leak happened towards the end of the procedure. Ascites resolved spontaneously over the next two days. Egress of fluid through the penile urethra into the amniotic cavity and an increase in amniotic fluid volume were confirmed using Doppler and B mode ultrasound respectively in both cases.

The purpose of intervention in both cases was twofold: (1) Attempt to treat the PUV on relieve pressure on the kidney and urinary bladder and prevent further damage to the kidneys. (2) To normalise amniotic fluid volume in the absence of which the fetus may developed a Potter sequence of anomalies. The pros and cons of such intervention were weighed against the otherwise universally poor outcome of renal failure and lung hypoplasia. In our first case, the pregnancy did carry on well for 6 weeks following the procedure. The renal failure that ensued thereafter was part of the natural history of this disease process. In the second case too, the purpose of the fulguration was the same as in the first. However, the need for reintervention/early delivery arose because of possible restenosis during the course of pregnancy, which again is a known complication of fetal cystoscopic fulguration and is the reason why some centers recommend putting in a stent through the hole that is made by the laser. This, however, carries a higher risk of posterior urethral fistulas and was, therefore, avoided. Moreover, the fact that the baby passed urine after birth and that there was severe reflux suggested that it was probably renal backpressure from the severe VUR that led to a fall in amniotic fluid volumes rather than actual restenosis. Nonetheless, had it not been for the

fulguration, this baby would not have survived the neonatal period. The procedure indeed turned out to be a timely step in both preventing Potter sequence and in salvaging the kidneys from further damage.

These two cases also help highlight some of the important challenges associated with this intervention: case selection, technical aspects of the procedure and prognostication before and after the intervention.

Firstly, the procedure requires a fully operational multidisciplinary team with a dedicated fetal therapy unit comprising of maternal–fetal medicine specialists, pediatric surgeons, pediatric urologists and care coordinators who liaison between the departments for seamless care delivery. Also, the procedure per se is technically demanding and requires meticulous planning, beginning with choosing the right patient and a well-chosen angle of entry depending on the placental and fetal position to allow optimum direct visualiation of the valve and thus the site of obstruction. There is often a marked degree of muscular hypertrophy around the bladder neck in LUTO and in the angle between the bladder axis and the upper posterior urethra. Earlier in gestation when there is little hypertrophy, the approach from the bladder to the urethra may be almost straight, while from early mid-trimester, it becomes progressively more difficult to see 'around the corner' as the angle increases and hypertrophy progresses [14]. This inability to obtain the perfect angle of entry may lead to incidental destruction of tissue in the bladder neck, possibly creating urological fistulae. Sananes et al. [23] reported about a 10% occurrence of these urological fistulae (urethra-cutaneous/urethero-rectal) in fetuses undergoing endoscopic fulguration of PUV.

Secondly, progression to renal failure antenatally or postnatally, despite intervention, is a big challenge: particularly considering the difficulty in accurately predicting this at the time of diagnosis/intervention. Urinary metabolites to assess fetal renal function have been widely used for the last 25 years [7, 24, 25]. Some earlier reports suggested that fetal serum beta 2 microglobulin may be a better predictor than fetal urinary biochemistry [26]. However, a recent systematic review concluded that there is insufficient evidence to recommend such invasive analysis before 24 weeks [7].

Among the predictors of postnatal renal outcomes, ultrasound parameters like renal cortical appearance and amniotic fluid have been shown to have the highest predictive value and accuracy as reported by Morris et al. [27]. In our experience of two cases, fetal urinary biochemistries and falling amniotic fluid trend were considered for selecting possible candidates for fetal cystoscopy. Urinary biochemistry confirmed the notion stated by the systematic review. However, the ultrasound notion was refuted, as both cases were similar in terms of ultrasound findings of the urinary system but had contrasting outcomes. Moreover, both the fetuses presented with bilateral hydroureteronephrosis and hyperechoic renal cortex.

There is still limited data to dictate the appropriate therapeutic intervention for fetal LUTO. The PLUTO trial [28] on vesico-amniotic shunting concluded that urinary bladder decompression could improve survival but not overall renal function. In 2011, a systematic review first suggested no improvement in perinatal mortality or morbidity when comparing fetal Cystoscopy (FC; n = 4) and Vesicoamniotic shunting (VAS; n = 13) [29]. In 2015, a multicenter observational study of 111 cases undergoing cystoscopy, shunt or expectant management reported improvement in survival rates at 6 months in fetuses with fetal intervention [30]. It also highlighted the superiority of fetal cystoscopy over vesico-amniotic shunt in preventing impairment of renal function of the survivors and postulated that cystoscopic fulguration improved urinary bladder cycling and facilitated a more physiological emptying of the bladder unlike shunting, which was at best a diversionary procedure. In 2017, another systematic review of 246 fetuses (112 Vesico-amniotic shunts; 134 expectant management) showed a positive effect of vesico-amniotic shunts on perinatal survival but no statistical difference in terms of 6-month to longer survival or postnatal renal function [31].

At our center, we offer fetal cystoscopy over vesicoamniotic shunting as the primary therapeutic option because it allows direct visualisation of the posterior urethra, differentiates posterior urethral valves from other causes for LUTO (urethral atresia, stenosis etc.), avoids frequent re-interventions required in shunt dislocation and is more physiological for release of obstruction and drainage [32].

Vinit et al. [33] in 2019 also conducted a retrospective study on 48 procedures (23 FC, 25 VAS) and reported no difference between fetal cystoscopy and vesico-amniotic shunt regarding survival, complication rates and long-term kidney function.

Our limited experience with these two cases and a few similar cases that did not opt for intervention, clubbed with the fact that fetuses in our series with spontaneous bladder rupture antenatally have shown good postnatal renal function also opens up the question as to whether a more pro-active approach regarding the timing of intervention is required rather than waiting for oligohydramnios to set in as is the norm now. However, we need large prospective multi-centric case series or better still, randomised control trials to conclusively tell us the merits and demerits of fetal intervention for LUTO. Until such evidence becomes available, fetal endoscopic fulguration of posterior urethral valves should still be offered as an experimental intervention (Table 1).

Table 1 Literature review of prenatally diagnosed cases of LUTO treated with fetal cystoscopy

References	Intervention	Number of cases	GA at diagnosis, procedure, delivery (weeks)	Complications	Outcomes
Quintero et al. [7]	FC + Endoscopic fulguration of PUV	1	19, 22, 31	PTL at 31 weeks	NND on Day 4
Quintero et al. [10, 11]	FC + Endoscopic fulguration of PUV + VAS	1	NS, 26, 35	Displaced VAS	ALIVE; discharged at PND 3 in excellent condition with normal creatinine levels
Welsh et al. [15]	FC	13	NS,21, NS	PROM (1): 10% Late spontaneous abortion (1): 10%	TOP (1):10% Live births (6): 60% IUFD (3): 30%
Ruano et al. [19]	FC	Total (n): 11 4/11: Urethral atresia 7/11: Endoscopic laser ablation	13, 21,33	PPROM (3/8): 37.5% Extremely preterm birth (2/8):25%	TOP (3/11): 26% Live births (5/8): 62.5% NND (3/8): 37.5%
Ruano et al. [20]	FC	Total (n): 6 3/6: Urethral atresia 3/6: Endoscopic laser ablation	12.5 +/− 0.9, 16, 1: 33 weeks due to oligo 2: 35 weeks 3: 36 weeks	NIL	TOP (3): 50% (all cases of urethral atresia) Endoscopic laser treatment: Live births (2/3): 66.6% Neonatal death due to megacystis microcolon intestinal hypoperistalsis syndrome (1/3): 33.3%
Sananes et al. [23]	FC + Endoscopic Fulguration of PUV	Total (n): 40 Endoscopic laser ablation:23	13.9 +/− 2.8, 18.6 +/− 3.4, NS	Urological fistula (4/40): 10%	Live births (14/23): 60.9%
Ruano et al. [22, 30]	FC	34	13.7 +/− 2.7, 18.5 +/− 2.9, 25.1 +/− 7.9	NS	TOP (12/34): 35.2% Survival at 6 months (13/22): 59.1%
Martinez et al. [21]	FC + Endoscopic fulguration of PUV	20	14.1–25.5, 18.1, 37.3	Urinary ascites (1/20): 5%	TOP (9/20): 45% Live births (11/20): 55% Follow up b/w 15–110 months Normal renal function (8/11): 72.7% Chronic renal failure awaiting transplantation (3/11): 27.3%
Sananes et al. [23]	FC	Total (n): 50 (2 excluded after the cystoscopy due to TRISOMY 18) Endoscopic Fulguration of PUV: 30/48 Urethral atresia:13 Urethral stenosis:5	NS, 19.4, 32.4	Umbilical vein laceration (1/30): 3% PERINEAL FISTULA (4/30): 13% EVISCERATION (1/30): 3% RECCURENCE (6/30): 20.0%	TOP (17/48): 35.4% IUFD (2/48): 4.2% Live births (29/48): 61% NND (11/48):22.9%

Table 1 continued

References	Intervention	Number of cases	GA at diagnosis, procedure, delivery (weeks)	Complications	Outcomes
Vinit et al. [33]	FC + VAS	Total no. of patients(n):21	17.1, 21.4, 35.6	MATERNAL: PROM (6):26%	TOP (7/21): 33%
		Total FC 23		PTL (1):6%	IUFD (2/21): 9.5%
				FETAL: Shunt migration (1):6%	Live births (12/21): 57%
				Evisceration (4):25%	
				Urinoma/fistula (4):25%	
				Bowel perforation (1):6%	
				Muscular hematoma (1):6%	

VAS vesicoamniotic shunt, *FC* fetal cystoscopy, *PUV* posterior urethral valves, *NS* not specified, *PND* postnatal day, *TOP* termination of pregnancy, *PROM* preterm rupture of membranes, *IUFD* intrauterine fetal death, *PTL* pre-term labor, *NND* neonatal death

Conclusion

Fetoscopic laser fulguration of PUV, although technically demanding, is a feasible option to treat LUTO in the Indian scenario. Although considered superior to vesico-amniotic shunting as it promotes physiological bladder cycling, several challenges limit its wider application in practice. Case selection still remains the biggest of them, particularly due to the lack of a specific test to reliably understand the degree of renal damage prior to the procedure. Lack of definite ultrasound or biochemical parameters antenatally to determine perinatal outcome is evident from our two cases that had similar pre-operative profiles but contrasting post-operative outcomes. Additionally, the procedure is technically challenging and has a steep learning curve, although future technical improvements may allow for decreased fetal morbidity and better postnatal outcomes. These challenges, combined with the scarcity of long term follow up data on operated cases would force us to consider the procedure as experimental, till more robust evidence becomes available. Prospective parents should be appropriately counseled along these lines before they decide to accept fetoscopic laser fulguration of PUV.

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