REVIEW ARTICLE

Interventions for Fetal Lower Urinary Tract Obstruction

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Abstract

Aims and objectives: To review intervention methods for fetal lower urinary tract obstruction (LUTO).

Background: Lower urinary tract obstruction is a group of congenital anomalies present in 2 to 3/10,000 live births and may be associated with 45 to 100% perinatal mortality. Prenatal ultrasound is the diagnostic tool for LUTO and also can be helpful for the selection of appropriate cases for antenatal treatment. Common ultrasonographic symptoms are distended bladder (megacystis), oligo/anhydramnios, hydronephrosis, and renal parenchymal changes especially in severe forms of LUTO. Recent studies in this field reported clinical scoring systems for LUTO instead of classic antenatal ultrasonographic criteria which allows for appropriate counseling and treatment of cases. Monitoring with serial ultrasonographic series, termination of pregnancy for selected cases, and prenatal fetal intervention are among management options of LUTO. *In utero* treatment is based on the possibility of removing the obstruction in the urethra and preventing renal damage as well as pulmonary hypoplasia by restoring the amniotic fluid volume.

Results: Currently, vesicoamniotic shunting (VAS) and fetal cystoscopy are main choices for fetal therapy in LUTO. Retrospective and prospective cohort studies and a relatively small randomized controlled trial have demonstrated that these procedures may possibly improve perinatal survival.

Conclusion: Future prospective trials may improve the efficacy of diagnostic criteria and timing for procedures and may provide us with more information about effect of LUTO on long-term renal performance during postnatal period.

Clinical significance: Diagnosing fetal LUTO and treating accordingly may improve postnatal renal functions and survival of the baby.

Keywords: Fetal therapy, Lower urinary tract obstruction, Prenatal ultrasonography.

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Background

Fetal lower urinary tract obstruction (LUTO) is a common term for various pathologies characterized by a dilated fetal bladder. Prenatal diagnosis plays critical role for early detection and treatment of LUTO. About 60% of the affected children requiring surgery for renal or urinary tract problems in their first 5 years of life may be identified by prenatal ultrasound.[1]

Prevalence and Etiology

The incidence of congenital LUTO is estimated to be 2.2–3.3/10,000 births and generally caused by mechanical or functional bladder outlet obstruction at the level of the urethra.[2] Studies have shown that posterior urethral valve (PUV) is the most common underlying etiology of LUTO (63%) in males, followed by urethral stenosis or atresia (17%) which is the most common cause of LUTO in females.[2,3] Data show that 28% of males with PUV have an increased lifetime risk for end-stage renal diseases.[4] Obstructive abnormalities related to Prune–Belly syndrome, prolapsing cecoureterocele, cloacal malformations, and caudal regression are other rare causes of LUTO.[5] Neurological causes associated with smooth musculature tone regulation of bladder and genetic anomalies, such as megacystis microcolon intestinal hypoperistalsis syndrome (MMHIS), are less common, and the latter is seen mainly in female fetuses.[6]

Diagnosis

Megacystis, pelvicalyceal dilatation, oligohydramnios/anhydramnios, and renal parenchymal changes, such as hyperechogenic kidneys, are prevailing diagnostic findings for LUTO.

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Megacystis, a distended urinary bladder, is present in 0.06% of pregnancies[7] and although the diagnosis can be made easily by ultrasound in the first trimester, management is difficult in such patients.[8] Typically, fetal bladder is detectable by 11–12 weeks' gestation on ultrasonography, confirming by demonstrating of umbilical arteries coursing along the lateral margin of the fetal bladder. In the first trimester, longitudinal bladder diameter (LBD) 7 mm or more characterizes enlarged fetal bladder.[5] There are different definitions of megacystis in second (after 18 weeks' gestation) and third trimesters but failure to empty an enlarged fetal urinary bladder over a period of 45 minutes or longitudinal diameter (in millimeters) greater than gestational age in weeks plus 12 are the mostly used criteria.[8]

Keyhole sign is referred as bladder wall thickening with associated posterior urethral dilatation which on ultrasound resembles a keyhole. While this sign was considered to be specific for PUV, studies suggested that this sign was not specific for PUV and may be also seen in other pathologies. Bernardes et al. reported that the sensitivity and specificity of increased bladder wall thickness

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and bladder dilatation were highly associated with the diagnosis of PUV rather than the keyhole sign.[9] In another review, Fontanella et al. notified that keyhole sign demonstrates high specificity (74%) but poor sensitivity (48%) for LUTO.

Hydronephrosis is a non-specific prenatal ultrasonographic feature for LUTO, and it is found in approximately 80% of non-obstructive uropathies.[10] A recent review reported the presence of hydronephrosis in only 40–50% of LUTO cases and this confirms low specificity of this sign for LUTO.[11] Up to 15% of PUV cases are associated with unilateral hydroureteronephrosis.[12] A 2009 systematic review of 13 articles about ultrasonographic findings suggestive of LUTO and predicting postnatal renal functions reported that abnormal sonographic appearance of the renal parenchyma characterized by the presence of renal cysts or increased renal echogenicity was predictive for poor postnatal renal function.[13]

First Trimester of Pregnancy and LUTO

Liao et al. reported that in the first trimester when there is fetal megacystis and the LBD is 7–15 mm, chromosomal abnormality risk in the fetuses but if there is no aneuploidy, spontaneous regression of the megacystis is seen in 90% of the cases. If the bladder diameter is >15 mm, the risk of chromosomal defects is about 10% and in the chromosomally normal group the condition is invariably associated with progressive obstructive uropathy.[14] But a new study (Fontanella et al.) also revealed that enlarged nuchal translucency (NT), rather than the LBD measurement, significantly increased the risk of complex megacystis, including fetuses with chromosomal and multiple structural abnormalities.[15] Another large prospective study by Syngelaki et al. reported trisomy 18 as the most common chromosomal abnormality for megacystis (33%), followed by trisomy 21 and trisomy 13, with 27% and 20%, respectively.[16] Considering these association with chromosomal abnormalities, studies recommend karyotype analysis for megacystis cases in first trimester if the LBD is equal to or more than 7 mm.

Second and Third Trimesters of Pregnancy and LUTO

Diagnosis of LUTO in second and third trimester may rely on ultrasonographic findings, such as megacystis, dilated posterior urethra (known as the keyhole sign), and either unilateral or bilateral hydronephrosis.[17] Megacystis in the second and third trimesters may be defined as an enlarged bladder with a size over the 99th percentile defined for gestational age,[18] and fetal bladder failing to empty during a period of 45 minutes,[19,20] yet there is no prospective study for determination of normal bladder dimensions during the second and third trimesters of pregnancy. A recent study[10] including 312 patients suspected megacystis from the 18th gestational weeks onward have showed poorer accuracy of LBD compared with bladder volume and severe megacystis was defined by a bladder volume >35 cm^3. Hereby, following investigations must be performed for patients in second and third trimester with detected megacystis: (1) Comprehensive ultrasonography targeting the level of obstruction, renal parenchymal structure, and gender determination; (2) amniotic fluid volume assessment; (3) diagnostic genetic evaluation as amniocentesis; (4) vesicocentesis.

Management

Management of LUTO is related to several factors: Amniotic fluid level, gestational week at diagnosis, degree of pyelectasis, renal cortical appearance, and fetal sex. Monitoring with serial ultrasonographic scanning may be optional if amniotic fluid and renal parenchymal appearance is normal. Termination of pregnancy is another alternative, particularly in severe cases with oligo/anhydramnios and renal cortical dysplastic changes observed at first and early second trimester.[6] Fetal intervention is another alternative for appropriate LUTO cases and also beneficial for decreasing mortality and morbidity due to pulmonary hypoplasia and renal failure in postnatal period.

The natural history of LUTO is highly variable. In a recent study, Fontanella et al. published a staging system for congenital LUTO capable of predicting the severity of the condition and its prognosis. A retrospective study involving 261 fetuses demonstrated that diagnosis of oligohydramnios at 20 weeks and bladder volume of 5.4 cm^3 are risk factors for predicting an adverse outcome.[21] Previous studies have reported similar results showing that the risk of perinatal death is more than 80% in second-trimester oligohydramnios with onset before 25 weeks' gestation and persisting for more than 14 days.[22,23]

Prenatal Interventions

Historically, the study of fetal interventions for LUTO began in San Francisco, California, in the early 1980s where investigators studied the effects of intervention in a fetal lamb. In 1982, studies regarding open fetal interventions and vesicoamniotic shunting (VAS) began to be reported in the literature.[24,25] At the present time, vesicoamniotic shunt and fetal cystoscopy are the main choices as fetal therapies for LUTO. Technical feasibility, placental site, bladder access, operator confidence, and the parent's choice may affect the type of the procedure. Both of these procedures are performed by ultrasound guidance, under maternal and fetal anesthesia and with parental consent.

Vesicoamniotic Shunts

Among all options, VAS is the most common technique performed for the management of LUTO and works by relieving pressure in the urinary system and minimizing further renal damage. It is a minimally invasive procedure, which involves ultrasonography-guided insertion of double-pigtail catheter into the fetal urinary bladder (proximal end) and the amniotic cavity (distal end).

Saccone et al. in a meta-analysis, including 10 articles with a total 355 fetuses, have reported that the overall survival was higher in the VAS group compared to the conservative group (OR: 2.54, 95% CI: 1.14–5.67). Sixty-four of one hundred and twelve fetuses (57.1%) survived in the vesicoamniotic shunt group compared to 52/134 (38.8%) in the control group. Five studies reported on postnatal renal functions between 6 months and 2 years of age. Rate of good postnatal renal function was higher in the vesicoamniotic shunt group compared to the conservative group (OR: 2.09, 95% CI: 0.74–5.9).[26] Nassr et al. reviewed studies which included 112 fetuses treated with VAS and 134 managed conservatively. This systematic review demonstrated significant difference between perinatal survival (OR: 2.54, 95% CI: 1.14–5.67), but there was no difference in 6- to 12-month survival (OR: 1.77, 95% CI: 0.25–12.71) or 2-year survival rates (OR: 1.81, 95% CI: 0.09–38.03).[27]

A study from Korea evaluated the perinatal outcomes of fetuses with LUTO who underwent VAS included 32 fetuses and overall survival rate was 68.8% (22 of 32). The rates of normal renal function were 40.6% (13 of 32) at 28 days and 40% (10 of 25) at 2 years after birth.[28]

Early VAS in fetuses with presumed LUTO may also be considered. Study investigating outcomes of VAS performed before 16 weeks of pregnancy in fetuses with severe megacystis diagnosed with LUTO showed beneficial effect of early intervention on long-term renal performance during postnatal follow-up.[29]

PLUTO Trial

Percutaneous VAS vs conservative management for fetal lower urinary tract obstruction [the percutaneous shunting in lower urinary tract obstruction (PLUTO) trial] is the only randomized trial investigating the performance of vesicoamniotic shunt for the management of LUTO. It was published in 2013 and included 31 women with singleton pregnancies complicated by LUTO. Pregnant women from UK, Ireland, and the Netherlands were recruited to this trial. Due to poor recruitment, the study was stopped early and only 31 patients were randomized. Sixteen of them were allocated to the vesicoamniotic shunt group and 15 to the conservative management group. Of the 16 fetuses performed VAS, 8 neonates survived to 28 days, compared with 4 from the 15 fetuses assigned to conservative management [intention-to-treat relative risk (RR) 1.88, 95% CI 0.71–4.96; $p = 0{\cdot}27$]. Although the study was stopped early, previous retrospective cohort studies on this subject had similar number of participants.

As a result, systematic reviews (including both retrospective studies and PLUTO trial) show that VAS improves perinatal survival 28 days postnatally, but its effect on long-term renal function is unclear.

Fetal Cystoscopy

Fetal cystoscopy is an alternative option to vesicoamniotic shunt and was firstly introduced in 1995.[30] It has some advantages; direct visualization of pathologies may be diagnostic and operation may be performed in the same session. Additionally, amnioinfusion is not required for cystoscopy compared to *in utero* VAS. Cystoscopy may also allow the placement of a transurethral catheter in case of urethral stenosis.[31] Ruano et al. reported that normal renal function was noticed in 13/34 fetuses in the cystoscopy group vs 12/61 in the conservative management group at 6-month follow-up (OR 1.75, 95% CI 1.05 to 2.92).[17] According to the results of studies comparing fetal cystoscopy and conservative management, perinatal survival rate was higher in cystoscopy group than conservative management.[17,30]

But for some cases, performing cystoscopy may be challenging due to acute angle of the bladder axis to the urethral axis. A new study by Vinit et al. showed that the bladder neck angle is approximately 15° higher in LUTO fetuses and the angle between the posterior urethra and the bladder axis averages 117° and they underlined the need for improvement of fetoscopes which may overcome the technical difficulties during the procedure.[32]

Sananes et al. investigating long-term outcomes after fetal cystoscopy for LUTO including 50 cystoscopies performed due to PUV (62%), urethral atresia (28%), and stenosis (10%), reported that cystoscopy was (91.4%) accurate in the diagnosis of the etiology of LUTO. Cystoscopy was associated with 54% long-term survival and normal renal functions were observed in two-thirds of the fetuses with PUV.[33]

Postnatal Outcomes of LUTO

Postnatal outcomes depend on severity of the disease and the effectiveness of the fetal intervention. Ruano et al. have reported that fetal VAS increased the postnatal survival rate up to 85.7%,[34] which is higher than the results of the previous studies (65%).[17,35] Standardized prenatal multidisciplinary management protocol for fetal LUTO was presented by Ruano et al., reporting as fetal intervention was positively associated with survival at 6 months of age (OR: 12.9, 95% CI: 2.28–89.40). Also, anhydramnios (OR: 0.12, 95% CI, 0.04–0.35), favorable fetal urine analysis (OR: 3.98, 95% CI: 0.63–25.15), and absence of renal cortical cysts (OR: 3.9, 95% CI: 0.66–24.2) were predictors of survival. Proposed staging system for fetal LUTO intervention by Ruano et al. is presented in Table 1.[36]

In a retrospective study including 89 fetuses with posterior urethral valves, Dreux et al. evaluated fetal urine biochemical markers (total protein, β2-microglobulin, sodium, chloride, glucose, calcium, and phosphorus) with postnatal glomerular filtration rate (GFR) at 10–30 years of age. This study showed that urine biochemistry had 87% sensitivity and 72% specificity for the prediction of postnatal renal function when a single marker (β2-microglobulin) was used and 93% sensitivity and 71% specificity when combination of β2-microglobulin and chloride was used, therefore, β2-microglobulin and chloride may be used for predicting postnatal long-term renal function.[37]

Conclusion

As a result, the decision to intervene for fetal LUTO is complex and requires multidisciplinary approach for diagnosis, management, and long-term follow-up. Before performing any treatment modalities, detailed counseling of the parents about the possible pros and cons of the procedure is necessary. A randomized trial and retrospective reviews showed higher perinatal survival rates for LUTO cases when a fetal intervention was performed, but long-term results on renal morbidity is somehow controversial. Also improving of proper interventions to them must be main target for future LUTO studies.

Table 1: Proposed staging system for fetal LUTO intervention

Parameters	*Stage 1*	*Stage 2*	*Stage 3*	*Stage 4*
Amniotic fluid index (after 18 weeks' gestation)	Normal	Oligo or anhydramnios	Oligo or anhydramnios	Anhydramnios
Renal echogenicity	Normal	Hyperechogenic	Hyperechogenic	Hyperechogenic
Renal dysplasia	Absent	Absent	Present	Present
Renal cortical cysts	Absent	Absent	Present	Present
Fetal urinary biochemistry	Favorable	Favorable over 3 serial samples	Unfavorable over 3 serial samples	Less than 27% bladder refilling 48 h after vesicocentesis
Recommendation for intervention	No intervention	Intervention	No intervention	No intervention

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