Fetal Intervention for Bladder Outlet Obstruction: Where Are We Now?

Marie-Klaire Farrugia MD MD(Res) FRCS(Ed(Paed.Surg)
Chelsea & Westminster and Imperial Hospitals, London
Chester J. Koh, MD, Texas Children’s Hospital, Houston

Congenital lower urinary tract obstruction (LUTO), posterior urethral valves (PUV) in particular, remains a leading cause of end-stage renal disease (ESRD) in children. This is in spite of prenatal diagnosis, pre-emptive postnatal care, and close renal and bladder follow-up, and irrespective of fetal intervention or otherwise. This controversial topic was discussed at the Society for Fetal Urology meeting in Dallas in September 2016, whereby it was felt that decision-making at key prenatal stages of the disease required a closer collaboration between Fetal Medicine and Pediatric Urology. An international survey of pediatric urologists was conducted between October 2018 and April 2019 – and distributed to members of the Society for Fetal Urology (SFU), European Society of Pediatric Urology sub-groups, British Association of Pediatric Urology (BAPU), Sociedad Iberoamericana de Urologia Pediatrica (SIUP), Australia Pacific Association of Pediatric Urology (APAPU), Brazilian School of Pediatric Urology (BSPU), Paediatric Urologist of Canadian (PUC), and the Chilean Pediatric Urology Group. Ninety-nine responses were obtained. Within the limitation of biased responses from urologists with an interest in fetal urology, 20% of urologists said they weren’t consulted at all when a prenatal diagnosis of fetal LUTO was made; whereas almost half of respondents would not be informed if the decision to shunt a fetus were made. Twenty per cent of pediatric urologists were consulted on no cases with prenatal LUTO that year; 60% were consulted on 1-5 cases, with the remainder consulted on 6 or more cases. Eighty-five percent of respondents had not recommended shunting for any LUTO cases. Fourteen percent recommended shunting in 1-5 cases, whereas one centre recommended shunting in 6 or more cases.

Respondents were queried on their indications for shunting (Fig.1) – almost half would shunt in response to a progressive decrease in amniotic fluid. Forty-six per cent did not use information from fetal urinalyses to assist their decision. A third of respondents would recommend shunting beyond 27 weeks gestation. Most of the respondents aimed to achieve a reduction in pulmonary hypoplasia by offering vesico-amniotic shunting (VAS) (Fig.2). This simple survey gave an insight into the world-wide variation in prenatal management of LUTO, with

(continued on next page)
From the Guest Editors (continued from previous page)

some centres not involving paediatric urology at all even when a decision to intervene prenatally was made. There was no clear consensus on indications, time window of intervention, or expected outcomes.

Hence the aim of this special edition of Dialogues is to bring together fetal interventionists and researchers, pediatric urologists and nephrologists, with the aims of creating closer collaborations and of establishing clear indications and well-defined timing for intervention—so that our combined outcomes can be more consistently favourable.

For this edition of Dialogues, we invited well-published authors to expand on their experiences with fetal LUTO and their ideas on future directions. Professor Mark Kilby, from the Fetal Medicine Centre, Birmingham Women’s and Children’s Foundation Trust, U.K. published the first randomized, multicenter control trial (PLUTO trial, 2006) to evaluate the effectiveness of VAS compared to conservative management. The study prematurely ended in 2010 because of poor recruitment. The PLUTO trial showed a higher survival to 28 days, 1 year, and 2 years, in fetuses treated with VAS compared to those with conservative management, and overall a very poor postnatal outlook (in terms of long-term childhood renal morbidity) irrespective of whether or not VAS was placed. Due to the small numbers of participants recruited (20% of the planned 150 pregnancies were randomized), the benefit of VAS was not conclusively proven by this trial.

Professor Rodrigo Ruano (Mayo Clinic Fetal Diagnostic and Therapeutic Center, Mayo Clinic College of Medicine, USA) presented a staging system of fetal LUTO, as a potential guide to patient selection for in-utero intervention, at the SFU meeting in Dallas. His article discusses a proposal for a prospective multicenter trial to standardize prenatal evaluation and management of fetal LUTO. His LUTO staging system has been correlated with postnatal outcomes in a single center retrospective study. In summary, Stage I LUTO is characterized by blader dilatation and bilateral hydronephrosis, but normal levels of amniotic fluid and favorable urinary biochemistry. Fetuses diagnosed with stage I LUTO are not candidates for fetal intervention as they will not develop pulmonary hypoplasia or ESRD; postnatal survival rate is almost 100%. Stage II LUTO comprises a group of fetuses that have preserved renal function at the time of diagnosis, in spite of the presence of oligohydramnios after 18 weeks of gestation. On ultrasound, hyperechogenic kidneys are usually present, but renal cortical cysts or dysplasia is absent. Results from fetal urine biochemistry should fall into the ‘favorable’ category. Ruano recommends fetal intervention for this stage of LUTO, with the objective of preventing both severe pulmonary hypoplasia and ESRD. The natural history of stage II LUTO is associated with poor outcomes without intervention. Stage III LUTO presents with anhydramnios (occasionally severe oligohydramnios), hyperechogenic kidneys with cysts and dysplasia with poor urine biochemistry. The usefulness of VAS at this stage is still uncertain. Stage IV LUTO consists of fetuses that have in utero renal failure who will typically succumb to their disease during the first weeks of postnatal life due to pulmonary hypoplasia or ESRD. On ultrasound, Stage IV LUTO has the characteristics of severe renal dysplasia with anuria; no intervention is recommended for these cases. Ruano et al. base the suggested MCT on this staging system, aiming to: (1) validate and standardize this prenatal staging system across multiple fetal centers, (2) standardize perinatal management of LUTO across fetal centers and (3) evaluate the impact of fetal intervention based on severity after standardization of prenatal care across fetal centers.

Kilby expanded on lessons learnt, in particular, that better patient selection and in-utero diagnosis and investigation was needed. “Megacystis” does not equate to LUTO, and the exclusion of chromosomal anomalies and other non- obstructive pathologies is key to patient selection. He discusses the benefits of fetal MRI, in particular to diagnosing established renal cortical dysplasia and lung hypoplasia, and explains the variation in the utilization of fetal urinalyses in directing therapy. Kilby accepts that classically, fetal specialists tended to treat cases with severe LUTO when marked oligohydramnios occurs. The rationale behind this choice was the consideration of fetal therapy as an option for increasing the chance of survival in fetuses with otherwise a life-threatening condition, by offering therapy to those cases with higher risk of perinatal death due to lung hypoplasia and prolonged oligohydramnios. This approach generated a bias for evaluating the role of fetal therapy in terms of postnatal renal function. In fact, when oligohydramnios occurs, deterioration of renal reserve may already be too severe to be improved or rescued by any intervention. As with advancing gestation, lung development and renal reserve deteriorate, choosing the best timing remains the central overarching therapy.

(continued on next page)
From the Guest Editors (continued from previous page)

Nassr, Koh and Belfort combine fetal medicine and pediatric urology expertise with a multidisciplinary approach at the Texas Children’s Hospital Fetal Center. Intervention is similarly based on a three-stage system. Their article describes the technical aspects of common fetal interventions. Professor Joseph Angelo, a pediatric nephrologist based at Texas Children’s Hospital, adds a nephrologic outcomes perspective. Following implementation of the classification system, the Texas Children’s group performed a retrospective chart review evaluating the relationship between LUTO stage and postnatal outcome. In this study of 42 fetuses with LUTO, 5 underwent termination of pregnancy and 1 had intrauterine fetal demise. The remaining 26 patients included 6 stage I; 18 stage II; and 12 stage III patients. No patients with stage I LUTO received fetal intervention, 100% of stage II and 25% of stage III underwent VAS. A greater percentage of neonatal deaths occurred in the stage III group (67%) compared with stage II (17%) or stage I (0%). 75% of surviving stage III pts required dialysis as neonates, and 100% were dialysis dependent by 1 year of age. Overall, 64% of pts were alive at 1 yr. Five pts underwent neonatal dialysis with 80% 1-year survival. Taken in aggregate, these data suggest that staging of LUTO based on several important components of fetal evaluation has utility in guiding fetal interventional decision making and potentially for predicting outcome in LUTO patients.

Michael Kurtz, from the Boston Children’s Hospital, investigates the causes of dislodgement and other complications of the vesico-amniotic shunts currently in use. He enlightens us on the team’s plans to develop a shunt to resist dislodgement and clogging, leaving a fetal vesicostomy which may be able to delay treatment of posterior urethral valves. They are studying a dumb-bell shaped, lumen-apposing silicone nitinol stent, woven in such a way that the thinner saddle in the middle is flanked by self-expanding soft flanges that serve to create a self-retaining system.

The Aftermath of PLUTO for the Assessment and Treatment of Congenital Bladder Neck Obstruction

Frederica Fontanella, MD1, C.M. (Katia) Bilardo, MD1,2 and Mark D. Kilby, DSc MD3,4

1Department of Obstetrics, Gynaecology and Prenatal Diagnosis, University Medical Center Groningen, University of Groningen, The Netherlands
2Department of Obstetrics, Gynaecology and Prenatal Diagnosis, Amsterdam UMC VU Medical Center, Amsterdam, The Netherlands
3Fetal Medicine Centre, Birmingham Women’s and Children’s Foundation Trust, Edgbaston, Birmingham
4Institute of Metabolism and Systems Research, College of Medical & Dental Sciences, University of Birmingham

Introduction

The acronym LUTO (Lower Urinary Tract Obstruction) refers to a relatively heterogenous group of congenital anomalies of the fetal urogenital tract characterized by poor fetal outcome. Owing to this heterogeneity the prenatal diagnostic work-up and antenatal management still need to be further pinpointed. In this manuscript, we aim to review the latest advances concerning the antenatal diagnosis and management, from fetal megacystis to congenital LUTO (bladder neck obstruction).

2. What is ‘megacystis’? Not all bladder neck obstruction. The exclusion of other pathologies.

The antenatal suspicion of congenital LUTO typically arises from the ultrasound (US) evidence of an enlarged fetal bladder, also called megacystis1. During the first trimester, fetal megacystis has been defined by a longitudinal bladder diameter (LBD) greater than 7 mm2.3. Beyond the 14th week of gestation, various and miscellaneous criteria have been reported in the literature to define megacystis, ranging from a bladder length >99th percentile for gestational age (in absence of a normogram), to the most commonly used definition of a fetal bladder failing to empty during a period of 45 minutes ultrasound examination 1,4,5,6.

The principal cause of megacystis is congenital LUTO, associated with bladder neck obstruction7,8. However, fetal megacystis can also be observed as corollary finding in fetuses with an underlying chromosomal abnormality, developmental abnormality and other miscellaneous...
Congenital Bladder Neck Obstruction (continued from previous page)

syndromal associations7,1,8,4(Figure 1). In the following paragraphs, we will further discuss each of these three groups.

Figure 1: First Trimester Megacystis. On the left, female fetus with a cloacal anomaly, presenting at 13 weeks of gestation with megacystis and longitudinal bladder diameter (LBD) of 34 mm. On the right, case of fetal megacystis in a male fetus with Trisomy 18, presenting with a LBD of 23 mm at 12 weeks of gestation.

Chromosomal anomalies in association with megacystis accounts for up to 13% of early diagnosis, of which trisomy 18 is the most frequent aneuploidy7,1. The pathological background of megacystis in autosomy trisomic fetuses has not yet been clarified. In fetuses with trisomy 18, previous studies have hypothesized a functional urethral obstruction related to the prostate hypoplasia, leading to obstructive uropathy9. Conversely, in fetuses with trisomy 13, obstructive uropathies have been very rarely reported, and the milder bladder enlargement compared to the other trisomic fetuses would rather suggest a different pathological background (mean LBD: 8.7 mm in Trisomy 13 vs mean LBD: 20 and 15 mm in Trisomy 18 and 21, respectively)7.

One of the most well-known congenital genetic syndromes associated with fetal megacystis is the megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)10, often associated with anomalies of the muscarinic receptors of smooth muscle (on bladder and bowel). This condition presents with classic LUTO signs such as hydrenephrosis and megacystis (together with dilated fetal stomach and dilated bowel loops in the second and third trimester), but a normal amount of amniotic fluid11.

Although its genetic base is heterogeneous and most of the cases are classified as sporadic, ruling out this syndrome by testing amniotic fluid digestive enzyme or fetal urinalysis has been advised before proceeding with antenatal intervention1.

The developmental anomalies more commonly detected among fetuses with megacystis are often complex anorectal malformations (ARM), involving anus, rectum and urogenital tract1. This group includes fetuses with a urethral and anal atresia, presenting with massive bladder distention, entailing a LBD twice the GA, and fetuses with multisystem structural anomalies, such as in the VACTERL association, OIES complex and Fraser Syndrome7.

To summarize, miscellaneous complex underlying conditions, associated with fetal megacystis and with additional structural anomalies or abnormal ultrasound finding, can be detected antenatally in up to 34% of fetuses. For this reason, whenever faced with a case of fetal megacystis, a detailed ultrasound scan with special attention at visualizing the spine, skeleton and heart is mandatory. According to the possible associated structural anomaly, a stepwise algorithm has been recently proposed to guide fetal specialists in the diagnostic work-up and rule out underlying conditions in suspected LUTO cases7.

Not all cases of megacystis demonstrate progression with advancing gestation as a spontaneous resolution can also occur during pregnancy3,12. According to Liao et al., spontaneous resolution occurs in approximately 90% of fetuses with LBD between 7 and 15 mm and normal karyotype7. According to a cohort study from the Netherlands, the optimal LBD cut-off for predicting the chance of spontaneous resolution in fetuses with megacystis diagnosed before 18 weeks’ gestation or thereafter is 12 mm and 22 mm, respectively12. The same authors reported that fetuses, identified early in pregnancy with a LBD of less than 12 mm, have a 70% chance of spontaneous resolution and have a favorable postnatal outcome, free from major urological anomaly, if resolution occurs before 23 weeks’ gestation12(Figure 2).

3. Epidemiology of congenital bladder neck obstruction.

The term LUTO refers to a group of anatomical anomalies leading to an obstruction of the lower urinary tract and including urethral atresia, urethral valves and urethral stenosis. LUTO occurs between 1 in 5,000 to 1 in 25,000 pregnancies, without accounting for cases where pregnancy is electively terminated, cases of intrauterine fetal demise (IUDF), or cases without a postnatal diagnosis13.

Posterior urethral valves (PUV) constitute the most common cause

Figure 2: First trimester Megacystis and spontaneous resolution. On the left, 12 weeks’ fetus with longitudinal bladder diameter (LBD) of 8.2 mm. On the right, resolution of megacystis in the same fetus at 13 weeks of gestation.

Figure 3: Second trimester LUTO. From the left to the right: keyhole sign; 3D sweeps of urinary pelvis, fetal ureters and megacystis; fetal kidneys with bilateral pyelectasia.

(continued on next page)
Congenital Bladder Neck Obstruction (continued from previous page)

of LUTO with a birth prevalence of 1 to 2 per 10,000 live male births
14,15. Urethral atresia, defined as complete infra-vesical obstruction that
obliterates the most distal portion of the prostatic urethra, represents
the most severe form of LUTO with very poor prognosis16. Urethral
stenosis consists of narrowing of the urethral lumen and constitutes a
less common and less severe variant of urethral atresia.

Depending on the severity of the obstruction, severe LUTO can
lead to the antenatal development of severe megacystis, bilateral hy-
donephrosis, renal dysplasia, and oligohydramnios, with secondary
lung hypoplasia and soft tissue deformities (leading to a ‘so called’
Potter sequence). On the contrary, fetuses with milder forms of LUTO
can even preserve normal amniotic fluid (AF) amount throughout preg-
nancy and favorable renal function after birth17. Overall, LUTO is as-
considered in as isolated, yields a limited diagnostic accuracy , as al-
less common and less severe variant of urethral atresia.

4. Ultrasound diagnosis of LUTO and sensitivity - specificity of
prognosis based upon ultrasound findings

The antenatal diagnosis of LUTO is classically based on the evi-
dence of megacystis, hydrenephrosis and dilated posterior urethra (also
known as the “keyhole sign”). Alternative associations of diagnostic
US criteria for LUTO have been also considered in the literature, such
as in a multicenter case-control study, published in 2015, where only
fetuses presenting with four specific US criteria (fetal megacystis, in-
creased bladder-wall thickness, bilateral hydrenephrosis and oligohy-
dramnios) were suspected for LUTO and treated antenatally. However,
even among this strictly selected group of fetuses, authors reported a
rate of 23% of false-positive diagnoses19. Moreover, an epidemiologi-
cal study reported in 2012 that one third of suspected LUTO are false-
positive diagnoses, with the majority of them with vesico-ureteral re-
draining fetal urine in the amniotic cavity.

Figure 4. Double pig-tailed catheter in situ
draining fetal urine in the amniotic cavity.

situ
draining fetal urine in the amniotic cavity.

flux (VUR) postnatally, an urological condition not amenable fo r in

fetal sex and evidence of oligohydramnios as shown in Table 1. A score
greater than 9.5 showed good accuracy for prospectively diagnosed
congenital LUTO22.

Once isolated LUTO is suspected, counseling and management
should be individualized depending on the expected outcome. Antena-
tal ultrasound prediction of postnatal renal function has been so far
considered problematic. A meta-analysis from Morris et al. has sug-
gested a mayor prognostic role of antenatal abnormal renal cortical
appearance and amniotic fluid volume, even though a large heterogeneity among the studies was highlighted in terms of the diag-
nostic test thresholds and outcome measurements23.

5. Further tests to aid diagnostic accuracy and prognosis including
fetoscopy.

Besides antenatal US, further aid to fine-tune the clinical approach
to fetal LUTO can be found in the use of MRI or fetoscopy for diag-
nostic purposes, as well as in the use of fetal biochemistry for impro-
v ing in the prediction of prognosis.

The use of MRI has already demonstrated good accuracy in de-
tecting associated anorectal malformations and in visualizing fetal
anatomy, in particular when oligohydramnios strongly limits the diag-
nostic accuracy of an antenatal US examination 24,25. MRI may also
play a role in predicting the prognosis of LUTO, for example, by evalu-
ating renal cortex integrity or lung development26.

Fetal cystoscopy can be used both as diagnostic and therapeutic
tool for the management of LUTO. In fact, fetal cystoscopy can allow
the direct visualization of the urethra, and both the eventual confirma-
tion and ablation of PUV. Although technically challenging to perform
and not therapeutic in fetuses with urethral atresia, fetal cystoscopy
yields high sensitivity (100%) and specificity (85.7%) for confirming
PUV27.

A number of biochemical markers, principally from fetal urine,
have also been investigated as predictors of renal function in LUTO.
Fetal urine analysis following serial vesicocentesis is commonly per-
formed before proceeding with fetal therapy, when sodium, chloride,
calcium, osmolality and beta-2 microglobulin are usually assessed. In
the literature, other markers have been also investigated such as trans-
forming growth factor beta, retinal binding protein, transforming growth
factor-â, epidermal growth factor, and more recently, the cystatin C
and matrix metalloproteinase (MMP-9)28,29. Studies on most of these
biomarkers are still limited and a systematic review by Morris et al.
showed that none of those analytes yields sufficient clinical accuracy
for predicting renal function30.

6. Therapeutic interventions: any change since PLUTO?

Since the first attempt in 1982, fetal therapy for LUTO has been
performed with the aim of bypassing the obstruction and of potentially
protecting from the clinical consequences of lung hypoplasia and renal
dysfunction31,32.

The classic antenatal intervention for LUTO consists in the ultra-
sound-guided percutaneous placement of a vesico-amniotic shunt
(VAS)(Figure 4). In 2006, the first randomized, multicenter control
trial (PLUTO trial) to evaluate the effectiveness of VAS compared to
conservative management has been conducted and prematurely ended
in 2010 because of poor recruitment. The PLUTO trial showed a higher
(continued on next page)
Congenital Bladder Neck Obstruction (continued from previous page)

By and large, the success of fetal therapy in congenital LUTO depends on both the timing and the group of fetuses to treat. Concerning the first point, a stepwise approach has been proposed to improve the detection of isolated LUTO and to only select fetuses with isolated PUV early in gestation. This algorithm encompassed three criteria (a LBD > 12 mm, normal nuchal thickness and absence of umbilical cord cysts) and showed good accuracy in selecting fetuses with isolated PUV, which could theoretically benefit more from an early fetal intervention.

Table 1. Clinical score for antenatal diagnosis of LUTO (22).

<table>
<thead>
<tr>
<th>US signs</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe megacystis (volume &gt; 35 cm³ or ascites)</td>
<td>4</td>
</tr>
<tr>
<td>Bilateral ureteral diameters</td>
<td>1.3 for each mm of ureteral size</td>
</tr>
<tr>
<td>Oligo- or anhydramnios</td>
<td>4</td>
</tr>
<tr>
<td>Fetal sex (male)</td>
<td>4</td>
</tr>
<tr>
<td>Referral before the 28th week</td>
<td>4</td>
</tr>
<tr>
<td>Risk of LUTO</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Score ≥ 9.5</td>
<td>96%</td>
</tr>
</tbody>
</table>

8. Future

Fetal cystoscopy represents nowadays a promising option for confirming the diagnosis of LUTO and eventually treat fetuses with PUV. However, its technical difficulties still limit its use. This is because the axis of the bladder and urethra makes visualization of the bladder neck difficult (if not impossible) and in order to visualize appropriately the bladder neck, the scope would need to have a specific curvature. Moreover, the insertion and manipulation of the device leads to leakage of urine into the abdominal cavity and to the subsequent loss of pressure within the bladder. For this reason, rapid performance of the procedure is crucial. More effort is therefore needed in the future for the development of fetal cystoscopes capable of making easier the visualization and entrance into the posterior urethra.

(continued on next page)
Congenital Bladder Neck Obstruction (continued from previous page)

The main technical improvements, required for the use of VAS, will consist in minimizing complications such as blockage or shunt migration. Currently, double-pigtails catheters represent the classic choice and two different types are currently available: the Harrison type (Cook Medical, Bloomington, IN) and the Rocket KCH one (Rocket Medical plc, Watford, England). Harrison catheter is often preferred before 18 weeks’ gestation, and the Rocket KCH one presents a lower risk of dislodgement (78% vs 30%)40. Double-basket catheters have been also recently developed as alternative to the double-pigtails ones. These ones have a small diameter that should reduce the risk of premature rupture of membranes, and not increase the risk of occlusion41.

To conclude, best timing and best candidates for fetal treatment of LUTO have not yet been clarified. For this purpose, further improvements in terms of diagnostic accuracy, prediction of prognosis, standardized approach to disease severity, technical advancements and a new RCT in the future will be needed in order to clarify the optimal management of fetal LUTO.

(continued on next page)
References


A Proposal for a Prospective Multicenter trial to Standardize Prenatal Evaluation and Management of Fetal Lower Urinary Tract Obstruction

Rodrigo Ruano MD, PhD; Elizabeth Ann L. Enninga PhD; Eniola R. Ibirogba, MBBS and Marie-Klaire Farrugia, MD

1Department of Obstetrics and Gynecology, Mayo Clinic Fetal Diagnostic and Therapeutic Center, Mayo Clinic College of Medicine, 2Chelsea & Westminster Hospital/ Imperial College Hospitals, London, England

Introduction

During fetal development, genitourinary abnormalities that block fetal bladder outflow tract are known as lower urinary tract obstruction (LUTO). Although rare, estimated to affect only 2.2-3.3 babies per 10,000 live births, LUTO is associated with a high perinatal mortality. Fetal anuria due to bladder outflow tract obstruction leads to oligohydramnios or anhydramnios and fetal renal dysfunction; the resulting pulmonary hypoplasia, severe renal impairment and end-stage renal disease (ESRD) account for the majority of LUTO mortality. LUTO is caused by a heterogeneous group of congenital anomalies that include: posterior urethral valves (most common), urethral atresia, urethral stenosis, prune belly syndrome and less commonly, anterior urethral valves, urethral diverticulum, congenital megalourethra, obstructing ureterocele, isolated megacystis, megacystis-megaureter or megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS). The etiology of LUTO has been correlated with postnatal survival although precise etiological diagnosis remains a challenge. Additionally, LUTO presents with a large spectrum of clinical manifestations possibly due to a variation in the severity of urethral obstruction (complete or partial). Given this complex interaction between etiology, severity and outcome, standardized prenatal evaluation is pivotal to appropriate selection of candidates that could benefit from prenatal management.

Currently, fetal ultrasound findings and urine biochemistry are used to guide clinical decision making and management of LUTO but it remains to be standardized across fetal centers. In this article, we will review what is known about the diagnosis and management of LUTO, introduce a standardized prenatal staging system and finally, discuss our proposal for a prospective multicenter trial to validate the prognostication and guide the management of LUTO.

Challenges of Fetal Diagnosis and Therapy in LUTO

Fetal intervention was proposed for severe LUTO to improve perinatal survival. Fetal therapy directly or indirectly addresses the two main consequences of LUTO, decreased amniotic fluid volume (oligo-hydramnios or anhydramnios) and increased pressure in the fetal uro-nephron system. Insufficient amniotic fluid impedes lung development (pulmonary hypoplasia) and results of experimental animal models suggest a causal relationship between in utero obstructive uropathy and renal dysplasia. Prenatal management options include: vesicocentesis, vesicoamniotic shunting, fetal cystoscopy or serial amnioinfusion. Vesicocentesis is a simple procedure in which the fetal bladder is punctured to aspirate urine; because repeated bladder drainage is required for sustained decompression with associated procedural risks, vesicocentesis is mostly used for diagnosis to obtain fetal urine samples for urinalysis.

Vesicoamniotic Shunting (VAS) is a procedure that allows continuous drainage (and sustained decompression) of the fetal bladder with a shunt. VAS involves placing a catheter in the fetal bladder (under ultrasound guidance) to drain the fetal urine for the remainder of gestation. This procedure, typically performed between 16 and 34 weeks of gestation improves amniotic fluid volume and hence decreases the severity of pulmonary hypoplasia; it does not however, correct the underlying urinary system pathology as 40% of LUTO neonates treated with VAS in utero eventually progress to end stage renal disease. Nevertheless, VAS is associated with improved overall survival (41-47% vs. 10% survival with no intervention) and is associated with improved overall survival (41-47%) with a shunt. VAS involves placing a catheter in the fetal bladder to drain the fetal urine for the remainder of gestation. This procedure, typically performed between 16 and 34 weeks of gestation improves amniotic fluid volume and hence decreases the severity of pulmonary hypoplasia; it does not however, correct the underlying urinary system pathology as 40% of LUTO neonates treated with VAS in utero eventually progress to end stage renal disease. Nevertheless, VAS is associated with improved overall survival (41-47% vs. 10% survival with no intervention). Some of the risks associated with VAS include shunt blockage and displacement, ascites, preterm labor and infections.

Fetal cystoscopy was introduced to address some of the technical limitations of VAS. Cystoscopy permits a more physiologic drainage of the obstructed bladder with the added benefit of etiological diagnosis and correction of the underlying LUTO pathology. The procedure involves percutaneous placement of a fetoscope (under ultrasound guidance) into the fetal bladder with direct visualization of the bladder outlet and dilated posterior urethra; posterior urethral valves (PUV), the most common etiology of LUTO is treated with laser fulguration of the occluding membrane. In a multicenter study, fetal cystoscopy was able to correctly diagnose the etiology of LUTO (i.e PUV or urethral stenosis) in 95% of cases; additionally, the 2 year postnatal survival rate following cystoscopy was 55% with 75% of infants demonstrating preserved renal function. Currently, the treatment of urethral stenosis by cystoscopy remains a challenge.

The objective of serial amnioinfusion is to restore the intrauterine amniotic fluid volume and promote healthy lung growth. The rationale being that aversion of the Potter sequence improves perinatal survival long enough for early initiation postnatal renal replacement therapy. Chronic dialysis is associated with a 90% survival rate when initiated in the first month of postnatal life. Serial amnioinfusion involves repeated infusion of normal saline into the amniotic cavity to achieve normal amniotic fluid volumes according to gestational age. The efficacy of this procedure is being investigated in the Renal Anhydranmios Fetal Therapy (RAFT) trial.

Prenatal sonography can accurately diagnose LUTO (sensitivity of 95%, specificity of 80%) but precise etiological diagnosis is difficult even with fetal magnetic resonance imaging. Fetal renal ultra-
Standardize Prenatal Evaluation (continued from previous page)

sound findings in LUTO include: bladder dilation, bilateral hydronephrosis and renal parenchymal changes (cortical cysts, renal dysplasia) (Figure 1). Fetal urinalysis also contributes to prenatal evaluation of LUTO since it indirectly reflects fetal renal function which is of prognostic significance. Different methods of collecting fetal urine samples have been reported, including single or serial vesicocentesis and pelvic puncture of the less compromised kidney11. Serial vesicocentesis is performed with the objective of obtaining fresh urine samples 21, 22. ‘Favorable’ urine biochemistry and, therefore, promising postnatal renal function and survival is defined as: urinary sodium < 100mEq/L, chloride < 90mEq/L, osmolarity <200mOsm/L and beta2-microglobulin <6mg/L 11, 22. Finally, amniotic fluid volume has also been correlated with survival in LUTO with severe pulmonary hypoplasia being the most dreadful complication of oligohydramnios/ anhydramnios. According to a recent systematic review, amniotic fluid volume and the appearance of the renal parenchyma are the most specific in defining prognosis with respect to long term survival and improvement of renal function in LUTO patients 23, 24.

Even with the diagnostic and prognostic information provided by prenatal imaging and fetal urinalysis, the lack of a standardized prenatal evaluation is a major limitation when selecting candidates that could benefit from fetal intervention. This limitation was especially reflected in the Percutaneous Shunting in Lower Urinary Tract Obstruction (PLUTO) multicenter, randomized control trial which failed to reach robust conclusions regarding the efficacy of VAS due to lack of specific inclusion criteria and poor recruitment 25, 26.

Standardization of Prenatal evaluation of LUTO

The current methods of diagnosis and management of LUTO have great promise for improving outcomes for fetuses; however, these procedures are not without maternal-fetal risks in addition to extensive medical costs. Furthermore, the lack of standardized evaluation and selection of candidates for fetal therapy limit the potential benefits of prenatal intervention. Prior to any therapeutic approaches for fetuses with LUTO, we believe that it is crucial to confirm the diagnosis, prognosticate the disease and select the appropriate candidates for intervention based on thorough risk stratification. Given the significant correlation between the perinatal outcomes, etiology and severity of LUTO, a corresponding staging system which combines ultrasound parameters with urological biomarkers is warranted.

The Ruano Prenatal Staging System classifies LUTO into four stages (Table 1) based on severity 21, 27 and parallels prognosis with management on a case by case basis (Figure 2) 28, 29. Fetuses presenting with LUTO with an associated anomaly (complex) tend to have poor outcomes and are therefore not considered candidates for fetal therapy. The LUTO staging system detailed below, has been correlated with postnatal outcomes in a single center retrospective study 21.

Stage I

Stage I LUTO consists of mild forms of fetal bladder outlet obstruction with incomplete obstruction, mainly urethral stenosis or partially obstructed posterior urethral valves based on information obtained prenatally from fetal cystoscopy and post-mortem autopsy findings 3, 30. Fetuses with stage I LUTO have bladder dilatation and, bilateral hydronephrosis, but normal levels of amniotic fluid and favorable urinary biochemistry. Fetuses diagnosed with stage I LUTO are not candidates for fetal intervention as they will not develop pulmonary hypoplasia or end stage renal disease (ESRD); postnatal survival rate is almost 100%. Any procedures to fix the partial urethral obstruction can be done postnatally by pediatric urologists.

Stage II

Stage II LUTO comprises a group of fetuses that have severe complete urethral obstruction (posterior urethral valves and urethral atresia)3, 30, but with preserved renal function at the time of diagnosis. Fetuses with Stage II disease often present with oligohydramnios or anhydramnios after 18 weeks of gestation. On ultrasound, hyperechogenic kidneys are usually present, but renal cortical cysts or dysplasia is absent. Results from fetal urine biochemistry should fall into the ‘favorable’ category (urinary sodium < 100mEq/L, chloride < 90mEq/L, osmolarity <200mOsm/L and beta2-microglobulin <6mg/L). Sequential urine sampling (maximum of three samples) collected over a 24-48 h interval is preferred to better reflect fetal renal function and avoid repeated sampling of stagnant urine when the initial results are not favorable 11, 21, 29, 31. Fetal intervention is warranted for this stage of LUTO and can include VAS or cystoscopy, with the objective of preventing both severe pulmonary hypoplasia and ESRD. The natural history of stage II LUTO is associated with poor outcomes without intervention. Larger multicenter trials are needed to assess the efficacy of VAS and fetal cystoscopy.

Figure 1a: Ultrasound image demonstrating a dilated bladder in a fetus with lower urinary tract obstruction at 13 weeks gestation.

Figure 1b: Ultrasound image suggestive of bilateral renal dysplasia at 25 weeks gestation.
Standardize Prenatal Evaluation (continued from previous page)

Stage III

Stage III LUTO presents with severe obstruction and abnormal fetal renal function. Anhydramnios (occasionally severe oligohydramnios), hyperechogenic kidneys with cysts and dysplasia are commonly observed on ultrasound evaluation. Urine biochemistries demonstrate poor renal function with minimal bladder filling rate after vesicocentesis 4. The use of cystoscopy is not suggested in this situation because of the small size of the bladder. The usefulness of VAS at this stage is still under investigation as it may improve lung development and perinatal survival to postnatal renal replacement therapy (chronic renal dialysis and renal transplant). Fetal intervention for Stage III LUTO patients has demonstrated little benefit with respect to renal function outcomes and survival analysis in a large, single center cohort 32. Thus, there is a need for improved treatment approaches for these cases of severe LUTO.

Stage IV

Stage IV LUTO consists of fetuses that have in utero renal failure who will typically succumb to their disease during the first weeks of postnatal life due to complications of severe pulmonary hypoplasia or ESRD. On ultrasound, Stage IV LUTO has the characteristics of severe renal dysplasia with anuria and a bladder filling rate < 27% (obtained by three-dimensional sonographic volume measurement) two days after vesicocentesis 29. No intervention is recommended for these cases; instead, palliative care or termination of pregnancy is the current management option. Serial amnioinfusion has been suggested in recent case reports for fetuses with renal failure33, 34 the goal of which is to improve pulmonary development in utero and prolong perinatal survival to early postnatal renal replacement therapy19. The patients described in recent case reports underwent weekly amnioinfusions starting in the second trimester with successful postnatal survival to peritoneal dialysis shortly after birth; however, long term outcomes of amnioinfusion are yet to be established.

Future Directions: Proposal for a Prospective Multicenter Trial to Improve Prenatal Management of fetal LUTO

Fetal interventions (VAS and cystoscopy) have yielded promising but inconclusive results with respect to postnatal outcomes of LUTO; fetal therapy seems to improve perinatal survival but long term outcomes are uncertain 31. Prenatal evaluation and diagnosis of LUTO is yet to be standardized and the indications for fetal intervention vary dramatically across fetal centers. Additionally, new clinical observations have correlated the large spectrum of clinical manifestations of LUTO with the variations in etiology and severity of urethral obstruction (complete vs. partial). Evidently, a standardized prenatal staging system is warranted.

Our proposed grading system based on longitudinal evaluation of sonographic renal parameters, fetal renal function and amniotic fluid volume 21, 27 is the rightful next step towards standardizing LUTO diagnoses to guide the selection of candidates for fetal intervention. The definition of ‘intrauterine fetal renal failure’ has also been proposed to identify fetuses with the most severe form of LUTO, which is associated with the worst prognosis 29. Utilizing a standardized protocol for LUTO diagnosis will provide a foundation for accurate assessment of the impact of fetal therapy on LUTO outcomes with future (randomized) trials. It will also promote the standardization of management and counselling across fetal centers. Finally, it will enable data gathering and assessment of long-term postnatal follow up of LUTO patients 28, 32.

We propose the initiation of a multicenter prospective trial and data repository using the suggested prenatal staging system of LUTO severity. The objectives of this trial are (1) to validate and standardize this prenatal staging system across multiple fetal centers, (2) to standardize perinatal management of LUTO across fetal centers and (3) to evaluate the impact of fetal intervention based on severity after standardization of prenatal care across fetal centers. In the proposed study, patients with a preliminary diagnosis of LUTO will be scheduled for an initial evaluation by a multidisciplinary team of experts including maternal-fetal intervention specialists, pediatric urologists, pediatric nephrologists, geneticists and fetal cardiologists.

Initial evaluation of potential study participants will include comprehensive ultrasonography, genetic testing and fetal echocardiogram towards LUTO staging. Eligible candidates diagnosed with isolated LUTO (with no additional fetal anomalies) at < 18 weeks of gestation will be counselled and offered the following management options: prenatal expectant management, fetal therapy or termination of pregnancy based on the staging system (FIGURE 2). Patients that elect to proceed with fetal intervention will be managed according to LUTO stage; vesicocentesis will not be considered during clinical evaluation due to
inconsistent information in the literature about this procedure before 18 weeks gestation. Fetal therapy (VAS or cystoscopy) will be followed by weekly ultrasound assessment of fetal status.

Mothers of fetuses diagnosed with isolated LUTO at 18 weeks but < 34 weeks of gestation with evidence of oligohydramnios who elect for fetal therapy will be offered vesicocentesis for fetal renal biochemistry. Candidates with favorable renal biochemistry will be managed according to LUTO stage with VAS or cystoscopy. Alternatively, candidates with unfavorable fetal renal function will undergo repeat vesicocentesis 48 hours after initial urine sampling; candidates with unfavorable urine biochemistry on repeat sampling will be offered VAS + serial amnioinfusions if stage III or serial amnioinfusions only if stage IV; whereas those with improved fetal renal function will be considered for fetal VAS or cystoscopy. LUTO patients that present after 34 weeks of gestation with evidence of oligohydramnios will be delivered and those with normal amniotic fluid volume will be followed with weekly ultrasounds until term. Patients with complex LUTO (LUTO associated with other anomalies) will need to undergo further investigations with fetal magnetic resonance imaging and accurate evaluation by the multidisciplinary care team to guide the individualized clinical approach to these cases.

After delivery, comprehensive clinical and laboratory evaluation will be performed on neonates with LUTO including renal ultrasound, voiding cysto-urethrogram (VCUG), serum electrolytes, renal function tests and urinalysis as part of standard postnatal care. Infants with LUTO will also be evaluated by a pediatric urologist and pediatric nephrologist to determine postnatal care and the need for surgical intervention. All patients with LUTO will be followed at least every 6 months until 24 months of life and then annually afterwards. Patients with renal impairment will be followed more frequently. Finally, neurodevelopmental status will be assessed with questionnaires directed at guardians of LUTO infants during follow up visits. Information from these routine examinations will be collected and documented to address the objectives of the proposed trial.

Successful completion of the proposed prospective trial will help standardize prenatal evaluation and management of LUTO across fetal centers and clearly define long term postnatal outcomes following fetal intervention. This study will establish clear selection criteria for fetal therapy which will serve as bedrock to assess the efficacy and potentially improve prenatal management of LUTO.

**Conclusion**

LUTO is a group of rare congenital anomalies characterized by anatomical or functional obstruction of the fetal urethra that affect 2-3 babies per 10,000 live births. Severe LUTO is associated with pulmonary hypoplasia and ESRD which accounts for the high mortality of this condition. Fetal therapy, including vesicoamniotic shunting, fetal cystoscopy and serial amnioinfusion have been proposed for LUTO management but the indications for these procedures vary across fetal centers. Standardization of LUTO diagnosis is crucial to the appropriate selection of candidates for adequate fetal intervention and perinatal management. We proposed a 4-stage LUTO classification that utilizes ultrasound and renal biochemistry to determine the appropriate management for LUTO on a case by case basis. Adopting this staging system in a prospective, multicenter trial will enhance the evaluation and comparison of perinatal and long term postnatal outcomes, and also standardize the management of LUTO across tertiary centers.

**Table 1: The Ruano Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Renal Ultrasound findings</th>
<th>Amniotic Fluid Volume</th>
<th>Fetal Urine Biochemistry</th>
<th>Possible Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal; no cysts or dysplasia</td>
<td>Normal</td>
<td>Favorable</td>
<td>Conservative management with weekly monitoring</td>
</tr>
<tr>
<td>II</td>
<td>Hyper-echogenic kidneys; no cysts or dysplasia</td>
<td>Oligohydramnios</td>
<td>Favorable - serial sampling if borderline</td>
<td>Cystoscopy or vesicoamniotic shunt</td>
</tr>
<tr>
<td>III</td>
<td>Hyper-echogenic kidneys; cysts and/or dysplasia</td>
<td>Anhydramnios or oligohydramnios</td>
<td>Unfavorable - serial sampling if borderline</td>
<td>Vesiocoamniotic shunt and amnioinfusion</td>
</tr>
<tr>
<td>IV</td>
<td>Hyper-echogenic kidneys with dysplasia</td>
<td>Anhydramnios and anuria</td>
<td>Unfavorable</td>
<td>Amnioinfusion</td>
</tr>
</tbody>
</table>

We proposed a 4-stage LUTO classification that utilizes ultrasound and renal biochemistry to determine the appropriate management for LUTO on a case by case basis. Adopting this staging system in a prospective, multicenter trial will enhance the evaluation and comparison of perinatal and long term postnatal outcomes, and also standardize the management of LUTO across tertiary centers.
Standardize Prenatal Evaluation (continued from previous page)

References

Fetal Lower Urinary Tract Obstruction and the Technical Aspects of Fetal Intervention: The Texas Children’s Hospital / Baylor College of Medicine Experience

Ahmed A. Nassr, MD, PhD1,2; Chester J. Koh, MD2,3; Michael A. Belfort, MD, PhD1,2

1 Department of Obstetrics and Gynecology, Texas Children’s Hospital and Baylor College of Medicine, Houston, Texas, USA
2 Texas Children’s Fetal Center, Houston, Texas, USA
3 Division of Pediatric Urology, Department of Surgery, Texas Children’s Hospital, and Scott Department of Urology, Baylor College of Medicine, Houston, Texas, USA

Introduction

Fetal lower urinary tract obstruction (LUTO) is a heterogenous group of conditions characterized by obstruction of the lower urinary tract at the level of the fetal urethra. It is a rare anomaly with a reported incidence of 2.2/10,000 live births1. LUTO is commonly diagnosed between 18-22 weeks' gestation at the time of the routine second trimester fetal anatomic survey. The most common cause of LUTO is urethral valves which are uniquely encountered in male fetuses. Other less common etiologies, such as urethral hypoplasia-atresia, urethral strictures, and ureteroceles, occur less commonly, but are seen in fetuses of either sex.

Fetal LUTO can present in two different ways, each with very different perinatal outcomes: (i) LUTO with normal amniotic fluid volume at mid-gestation, and (ii) LUTO with oligohydramnios-anhydramnios at mid-gestation. These two presentations define the varying degrees of severity on the disease spectrum, with almost normal perinatal survival in the first group, and frequently lethal outcomes in the second group.

With regard to renal morbidity, both groups can present with severe renal impairment requiring initiation of renal replacement therapy in the early neonatal period. While the degree of renal morbidity is roughly proportionate to the severity of the LUTO, a recent study at our institution on the outcome of fetal LUTO with normal amniotic fluid volume at mid-gestation showed that the majority of these babies had some degree of chronic kidney disease by the age of two years, with only 11% having normal renal function2.

Role of Fetal Intervention in Cases of LUTO

Several antenatal treatment options have been proposed to relieve LUTO and restore normal amniotic fluid volumes. These include vesicoamniotic shunt placement and fetal cystoscopy. The only randomized clinical trial that has evaluated the effectiveness of vesicoamniotic shunts for prenatally diagnosed LUTO was ended early for its inability to recruit sufficient numbers of patients, and unfortunately did not answer that question3,4. Systematic reviews have shown a survival advantage after placement of a vesicoamniotic shunt at mid-gestation. These two presentations define the varying degrees of severity on the disease spectrum, with almost normal perinatal survival in the first group, and frequently lethal outcomes in the second group.

With regard to renal morbidity, both groups can present with severe renal impairment requiring initiation of renal replacement therapy in the early neonatal period. While the degree of renal morbidity is roughly proportionate to the severity of the LUTO, a recent study at our institution on the outcome of fetal LUTO with normal amniotic fluid volume at mid-gestation showed that the majority of these babies had some degree of chronic kidney disease by the age of two years, with only 11% having normal renal function2.

Role of Fetal Intervention in Cases of LUTO

Several antenatal treatment options have been proposed to relieve LUTO and restore normal amniotic fluid volumes. These include vesicoamniotic shunt placement and fetal cystoscopy. The only randomized clinical trial that has evaluated the effectiveness of vesicoamniotic shunts for prenatally diagnosed LUTO was ended early for its inability to recruit sufficient numbers of patients, and unfortunately did not answer that question3,4. Systematic reviews have shown a survival advantage after placement of a vesicoamniotic shunt at mid-gestation. These two presentations define the varying degrees of severity on the disease spectrum, with almost normal perinatal survival in the first group, and frequently lethal outcomes in the second group.

With regard to renal morbidity, both groups can present with severe renal impairment requiring initiation of renal replacement therapy in the early neonatal period. While the degree of renal morbidity is roughly proportionate to the severity of the LUTO, a recent study at our institution on the outcome of fetal LUTO with normal amniotic fluid volume at mid-gestation showed that the majority of these babies had some degree of chronic kidney disease by the age of two years, with only 11% having normal renal function2.

Regarding fetal cystoscopy and fetal cystoscopic fulguration of the valves, although promising, this procedure is still limited by the limited availability of appropriate instruments and the high rate of fistula formation. With the development of purpose-built fetal cystoscopes with the correct curvature, and with appropriately designed trials, therapeutic cystoscopy may become a potential option in the future.
Technical Aspects of Fetal Intervention

Among the most common complications⁵. Shunt dislodgment can be external into the amniotic sac or internal into the fetal bladder. In some cases, the amniotic end of the shunt becomes displaced into the peritoneal cavity creating a vesico-peritoneal shunt with subsequent development of urinary ascites. A recent study from our institution that compared the dislodgment rates of both types of shunt demonstrated that the Rocket shunt was associated with less likelihood of dislodgment compared to the Harrison shunt⁷.

Regardless of the shunt type, the following technical steps should be considered for successful intervention:

Combination of atropine, fentanyl and vecuronium in doses adjusted for estimated fetal weight is commonly administered intramuscularly (using a 22-gauge needle) before shunt placement. The purpose of administering these medications is to address possible fetal pain, avoid fetal movements during the procedure and to counteract the reflex bradycardia that may potentially occur during fetal intervention.

For successful placement of the shunt, ultrasound-guided amnioinfusion using adequate amount of warm Lactated Ringer’s solution mixed with an antibiotic (Nafcillin) is required. This will ensure better ultrasound visualization and creation of enough space for deployment of the amniotic end of the shunt. The site for amnioinfusion should be carefully selected and the tip of the needle should be clearly visualized to avoid inadvertently infusing fluid outside the amnion that can cause chorioamniotic separation or into the fetal subcutaneous tissue.

Before introduction of the shunt trocar, color Doppler should be applied to the suggested entry site in the uterine wall to avoid puncturing a major uterine vessel especially in cases of anterior placenta where lateral entry is usually required.

Direct introduction of the trocar into the fetal bladder should be avoided as this may lead to deployment of the distal end of the shunt into the uterine wall. Instead, the trocar should be directed into an amniotic fluid pocket and then advanced into the fetal bladder, preferably the lower aspect, to allow for enough space for successful shunt deployment.

Correct placement should be confirmed by ultrasound visualization of the internal and external ends of the shunt (Figure 2). In difficult cases, a small fetoscope can be introduced through the shunt cannula to confirm the successful placement.

Antenatal Evaluation, Staging and Management of LUTO Case

The aim of antenatal evaluation is to provide parents of a fetus with LUTO a realistic overview regarding the outcome of their pregnancy. This will aid the counseling process and will help select those fetuses who might benefit from a prenatal intervention. At our center, all patients with a prenatal diagnosis of LUTO undergo a standardized multidisciplinary evaluation comprising:

1. Comprehensive ultrasound
2. Fetal echocardiography
3. Genetic consultation and testing
4. Evaluation of renal function (biochemistry, evaluation of fetal bladder refill and ultrasound parameters)
5. Consultation with maternal fetal medicine, pediatric nephrology and pediatric urology specialists

We classify LUTO according to a three stage system (Table) that is based on the volume of amniotic fluid, the fetal urinary biochemical markers, and prenatal ultrasound criteria: Stage I (low risk for pulmonary hypoplasia and low risk for progressive renal damage); Stage II (at risk for severe pulmonary hypoplasia and progressive renal disease); and Stage III (current evidence of severe renal disease in-utero)⁸.

Stage I cases are typically followed expectantly with ultrasound examination on a weekly basis in order to monitor amniotic fluid volume. These patients are not offered fetal intervention since there is an expectation of excellent perinatal survival. For Stage II cases, fetal intervention is usually offered after thorough evaluation and counseling. Cases with stage III LUTO are unlikely to benefit from prenatal intervention and hence is rarely offered in these cases. However, the role of serial amnioinfusion in improving perinatal survival in specific cases is currently being investigated.

LUTO cases in female fetuses may point to a more complex underlying etiology (e.g. cloacal anomalies, bowel abnormalities) and an extensive workup (including amnioinfusion to improve ultrasound imaging, and fetal MRI) to exclude associated major abnormalities or other complex etiologies, is recommended before considering fetal intervention.

Figure 2: Prenatal ultrasound showing a fetal bladder shunt in place
Technical Aspects of Fetal Intervention (continued from previous page)

**Conclusion**

Fetal LUTO is associated with significant perinatal mortality and morbidity which tend to be less severe in the group of fetuses who present with normal amniotic fluid volume during mid-gestation. Appropriate antenatal evaluation and staging are of utmost importance for prognosticating the cases and selecting the candidates who may benefit for prenatal interventions. Further research is needed for evaluating better markers for prediction of fetal renal function, as well as the development of more efficient surgical devices that may allow for earlier interventions and possibly fetal cystoscopic procedures as well.

**References**


**Table: Staging of Fetal LUTO Based on Diseases Severity**

<table>
<thead>
<tr>
<th>Fetal parameter</th>
<th>Fetal LUTO stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I LUTO</td>
</tr>
<tr>
<td>Amniotic fluid volume</td>
<td>Normal</td>
</tr>
<tr>
<td>Renal echogenicity</td>
<td>Within normal</td>
</tr>
<tr>
<td>Renal cortical cysts</td>
<td>Absent</td>
</tr>
<tr>
<td>Corticomedullary differentiation</td>
<td>Preserved</td>
</tr>
<tr>
<td>Urine biochemistry</td>
<td>Favorable</td>
</tr>
<tr>
<td>Fetal intervention</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>
Outcomes in Congenital Lower Urinary Tract Obstruction
Auda Plaud, MD, Fellow, Pediatrics-Renal Section
Baylor College of Medicine/Texas Children’s Hospital
Joseph R. Angelo, MD, Assistant Professor of Pediatrics-Renal Section

Introduction
Fetal lower urinary tract obstruction (LUTO) is a rare congenital genitourinary tract abnormality occurring in approximately 3.3 in 10,000 live births and carries a high risk of morbidity and mortality.\(^1\)\(^2\) Fetal intervention, including vesicoamniotic shunting (VAS) and fetal cystoscopy, has been proposed as a way to improve fetal lung growth as well as reduce the negative effects of obstruction on renal development. However, fetal intervention carries risks, including premature rupture of membranes, premature delivery and fetal death.\(^3\) While these interventions certainly can be successful in restoring the flow of urine into the amniotic space, data regarding the impact of fetal intervention on long term outcomes, particularly renal outcomes, in this setting are lacking.

Several factors contribute to difficulties in establishing a strong correlation between fetal intervention for LUTO and postnatal outcomes. First, there are multiple causes of LUTO, including posterior urethral valves (most common), urethral atresia, urethral stenosis and prune belly syndrome, and it is not clear whether these distinct etiologies have variable pathophysiologic impact on renal development. Second, the gestational timing at which obstruction occurs and degree of obstruction can contribute significantly to abnormalities in renal development as renal morphogenesis may be particularly susceptible to alterations in urinary flow. Third, while disruption of fetal urinary flow likely contributes to abnormal kidney development, other primary congenital renal anomalies, such as renal hypoplasia and cystic dysplasia, are frequently seen in association with LUTO. This association is consistent with the CAKUT (congenital anomalies of the kidney and urinary tract) model of renal and genitourinary development. Together, the aforementioned factors result in a highly heterogeneous patient population, confounding studies examining the relationship between intervention and outcome.

Postnatal Renal Outcomes following VAS
One landmark study evaluating postnatal outcomes following fetal intervention is the PLUTO (percutaneous vesicoamniotic shunting versus conservative management on lower urinary tract obstruction) trial. This randomized controlled trial reported that there was a trend toward improved perinatal survival at 28 days for those who had percutaneous VAS, although it was not statistically significant (50% vs. 26%, \(p=0.27\)). No significant difference in the incidence of end-stage renal disease (ESRD) was reported, although none of the conservative management group achieved normal renal function at 2 yrs compared to two in the VAS group.\(^4\) The results of this study also suggest that there may be a differential improvement in lung compared to kidney development following restoration of amniotic fluid flow. In another retrospective study that evaluated 32 fetuses, all of whom underwent VAS, there was 68% perinatal survival, with normal renal function in 40% at 28 days. At 2 yrs, there was 52% survival with 40% normal renal function. These results contrast with the PLUTO trial perhaps due to the fact that median gestational age at intervention was earlier, 16 vs 20 weeks, and gestational age at birth was higher, 35.5 vs 34.6. This study may suggest an added benefit of VAS in preventing neonatal ESRD; however, no strict selection criteria were applied prior to VAS\(^5\). Other recent outcome data supports fetal intervention in cases of LUTO and emphasizes the importance of continuing to develop prenatal markers of postnatal outcome. For example, a recent meta-analysis of nine studies, reported increased likelihood of survival for LUTO patients undergoing VAS than those managed conservatively (OR: 2.54, 95% CI: 1.14–5.67). In sub-group analysis, VAS was associated with higher perinatal survival among fetuses with unfavorable fetal urinary chemistry but not among those with favorable fetal urinary chemistry. This data highlights the need for accurate clinical tools that can be applied in selecting which patients will benefit most from fetal intervention.\(^6\)

Using LUTO Severity to Predict Postnatal Outcomes
In order to better standardize and define LUTO severity, a classification system based on disease severity was developed at the Texas Children’s Fetal Center. This schema is discussed in detail by Nassr et al in this edition of Dialogues in Pediatric Urology and is summarized in Figure 1 below. Following implementation of this classification system, the Texas Children’s group performed a retrospective chart review evaluating the relationship between LUTO stage and postnatal outcome. In this study, 42 total LUTO cases were seen in the study period from 2012 to 2016. Five underwent termination of pregnancy and 1 had intrauterine fetal demise. Therefore, 36 pts were evaluated. By stage there were: 6 stage I; 18 stage II; and 12 stage 3 patients. Regarding intervention, no patients with stage I LUTO received fetal intervention, 100% of stage II and 25% of stage III underwent VAS. A greater percentage of neonatal deaths occurred in the stage III group (67%) compared with stage II (17%) or stage I (0%). 75% of surviving stage III pts required dialysis as neonates, and 100% were dialysis dependent by 1 year of age. Overall, 64% of pts were alive at 1 yr. Five

(continued on next page)
Outcomes in Congenital LUTO (continued from previous page)

pts underwent neonatal dialysis with 80% 1-year survival.7 Taken in aggregate, these data suggest that staging of LUTO based on several important components of fetal evaluation has utility in guiding fetal interventional decision making and potentially for predicting outcome in LUTO patients.

Further support for the utility of establishing prenatal markers of postnatal renal function comes from other studies that have evaluated the predictive value of several of the parameters included in the above described LUTO staging system. A 2009 systematic review by Morris et al supported the predictive value of increased parenchymal echogenicity and renal cystic changes on postnatal serum creatinine. Similarly, the same systematic review found that oligohydramnios at the time of LUTO diagnosis was predictive of poor neonatal renal function.8 Interestingly, a retrospective review of data from the North American Fetal Therapy network showed that one third of children went on to require renal replacement therapy despite the presence of normal amniotic fluid volume at mid-gestation, supporting the concept that while fetal intervention to restore amniotic fluid is beneficial for lung development the protective effect for the kidneys may be less notable.9

Regarding biochemical markers, a 2018 study by Dreux et al demonstrated an association between fetal urine sodium, calcium and beta-2 microglobulin and long term renal function in LUTO survivors.10 Fetal urine beta-2 microglobulin has also been associated with decreased glomerular number while fetal serum beta-2 microglobulin has been associated with renal dysplasia as well as clinically correlating to postnatal serum creatinine.11,12

While some data does support the utility of the above noted anatomic and biochemical markers, they are by no means perfect predictors of postnatal renal function, emphasizing the need for further study of other anatomic and biochemical indicators. From an imaging standpoint, diffusion weighted magnetic resonance imaging with apparent diffusion coefficient has been shown to correlate with postnatal serum creatinine.13 Biochemically, fetal urinary collagen peptides have been noted to predict postnatal renal function in the setting of posterior urethral valves.14 Further study of these and other potential imaging and laboratory measures is needed in order to increase the ability of providers to predict not only postnatal survival but also long term renal function.

Conclusions

Current literature shows contrasting results with regard to fetal VAS and postnatal outcomes likely related small sample sizes and a heterogeneous population of patients. While it remains difficult to estimate postnatal renal function based on fetal anatomic and biochemical markers with certainty, current data supports the use of prenatal LUTO staging as a clinically useful tool as LUTO staging is associated with both neonatal survival and the need for dialysis. Building on the conceptual framework of a staging system, there is potential to develop more robust predictive models of postnatal outcome for prenatal LUTO based on the integration of newer imaging and biochemical parameters. A staging system that improves our ability to better predict outcomes in this population would allow for standardization in LUTO outcomes research, improve accuracy in patient selection for fetal intervention, provide prospective clinical data that would assist in the timely provision of postnatal care, and help families in making decisions and being prepared for the short and long term sequelae of fetal LUTO.

References

Improving the Vesicoamniotic Shunt for Fetal Lower Urinary Tract Obstruction

Michael Kurtz, MD, MPH
Boston Children’s Hospital, Department of Urology, Maternal Fetal Care Center

Restoration of physiologic amniotic fluid volume and composition to permit normal lung development has been the goal of fetal therapy for lower urinary tract obstruction (LUTO) since the advent of fetal surgery.1,2 Some of this pioneering research persists today in vesicoamniotic shunting (VAS). Other procedures, such as fluoroscopic fetal antegrade pyelography3, have been reconsidered as technology has made diagnosis more precise and as the same innovators critically analyzed their outcomes. While much has changed, there have been no innovations in VAS placement beyond systems that rely on thin extruded plastic tubes since the 1980s.

The effectiveness of fetal VAS was addressed in the largest, and likely only randomized study to be conducted in this condition, the PLUTO trial.4 It was limited by being underpowered, as well as contamination by crossover. Nonetheless, on the intention to treat analysis the odds of 30-day survival were over 3-fold greater in babies who received a VAS versus observation alone. This is demonstrated in metanalysis as well.5 We know that numerous complications can result from fetal VAS placement. Transient ascites is often present,6 even with fetal bladder aspiration. Shunts are associated with preterm rupture of membranes,7 which can lead to the most difficult clinical circumstance: a baby born with severe renal disease with a birthweight that does not permit peritoneal dialysis. While there has been a turn to avoiding shunts entirely, and treating the valves directly in utero via fetoscopy,7 there are sobering outcomes as well.8 That leaves the original procedure, shunting, as the current standard for fetal intervention for severe fetal LUTO.

Enthusiasm for shunting is reasonably tempered by device-related complications. Vesicoamniotic shunts, especially Harrison Fetal Bladder Stent, are known to dislodge.9 We have sought to develop a shunt to resist dislodgement and clogging, leaving a fetal vesicostomy which may be able to delay treatment of posterior urethral valves. We are studying a lumen-apposing silicone nitinol stent (Figure 1). It is woven in such a way that the thinner saddle in the middle is flanked by self-expanding soft flanges that serve to create a self-retaining system. We tested the two commercially available shunts against this prototype, measuring force needed to extract shunts in a simulated abdominal wall in an aqueous environment. The Harrison Stents dislodge at approximately 0.5 newtons, a Rocket KCH Fetal Bladder Catheter at 2.1 newtons, and the prototype shunt at 2.6 newtons. In addition, lowering the profile may resist manual dislodgement by fetal grasping of it, as there is simply less shunt to grab. These characteristics could be anticipated from the known shunt properties; whereas the Harrison Stent is smaller, at 5Fr, and soft, the Rocket KCH shunt is larger, and stiffer. It is so stiff that care must be taken to insert it properly, prompting a recent Urgent Field Safety Notice to not use the device should kinking be encountered.10

An ideal device would leave an epithelialized vesicostomy, which would allow for prompt device removal after birth and avoid the need for bladder drainage with a foreign body. Most babies with posterior urethral valves certainly do not need a vesicostomy, but the most severely affected babies, those having shunts for Stage II-III LUTO, are often born before term and this makes valve ablation difficult. Transurethral resection can result in stricture,11 and is particularly challenging with a tiny urethra. Long durations of indwelling catheters pose neonatal candidial infections, and so we designed our shunt to leave an approximately 16Fr epithelialized lumen postnatally. In early testing in Dorset lambs, this seems to be the case at term.

The fate of the bladder after shunting is unclear. There has long been concern that the placement of a shunt results in bladder fibrosis. More likely, based on animal data, the true pathophysiology is that the shunt fails to rescue severely affected bladder. As shown in obstruction of 60-day lambs, which corresponds to approximately 17 weeks human gestation, a fully obstructed bladder lead to muscular thickening as well as fibrosis, unchanged by shunt placement.12-13 As at the dawn of shunting, the primary indication for VAS placement is related to the primary threats to perinatal survival, anhydramnios and pulmonary hypoplasia, with renal concerns secondary and bladder concerns tertiary.

As at the dawn of shunting, the primary indication for VAS placement is related to the primary threats to perinatal survival, anhydramnios and pulmonary hypoplasia, with renal concerns secondary and bladder concerns tertiary.

As physicians we must seek balance. Mothers may experience distress from the diagnosis of fetal hydronephrosis alone,14 and one could only imagine it is far more severe when LUTO is at hand. While many babies with LUTO do not require any form of prenatal intervention, for those that do repeating fetal shunting from dislodged stents can be avoided through better design. We owe these mothers and babies a shunt which can accomplish the goals we know to be associated with better fetal outcomes in a way that minimizes morbidity.

References

(continued on next page)


10. R. URGENT FIELD SAFETY NOTICE. 2019. p. URGENT FIELD SAFETY NOTICE.


