

## Congenital urinary tract obstruction

Cheung, Ka Wang; Morris, Rachel Katie; Kilby, Mark David

DOI:

[10.1016/j.bpobgyn.2019.01.003](https://doi.org/10.1016/j.bpobgyn.2019.01.003)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Cheung, KW, Morris, RK & Kilby, MD 2019, 'Congenital urinary tract obstruction', *Best Practice & Research: Clinical Obstetrics & Gynaecology*, vol. 58, pp. 78-92. <https://doi.org/10.1016/j.bpobgyn.2019.01.003>

[Link to publication on Research at Birmingham portal](#)

### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### Take down policy

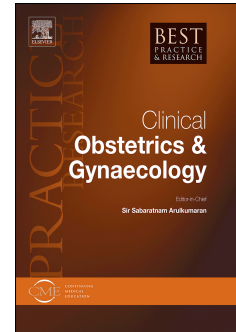
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

# Accepted Manuscript

Congenital urinary tract obstruction

Ka Wang Cheung, Rachel Katie Morris, Mark David Kilby



PII: S1521-6934(18)30202-5

DOI: <https://doi.org/10.1016/j.bpobgyn.2019.01.003>

Reference: YBEOG 1889

To appear in: *Best Practice & Research Clinical Obstetrics & Gynaecology*

Received Date: 11 September 2018

Revised Date: 1 January 2019

Accepted Date: 7 January 2019

Please cite this article as: Cheung KW, Morris RK, Kilby MD, Congenital urinary tract obstruction, *Best Practice & Research Clinical Obstetrics & Gynaecology*, <https://doi.org/10.1016/j.bpobgyn.2019.01.003>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title page

Title: Congenital urinary tract obstruction

Ka Wang Cheung <sup>a,b</sup>

Rachel Katie Morris <sup>b,c</sup>

Mark David Kilby <sup>b,c</sup>

a: Department of Obstetrics and Gynaecology, Queen Mary Hospital, the University of Hong Kong, Hong Kong SAR, China.

b: The Fetal Medicine Centre, Birmingham Women's and Children's Foundation Trust, Edgbaston, Birmingham B15 2TG, UK.

c: The Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT.

Corresponding Author:

Ka Wang Cheung

Address: 6/F, Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong

Kong

Telephone: (852) 22554517

Fax number: (852) 28550947

Email: [kelvincheung82@hotmail.com](mailto:kelvincheung82@hotmail.com)

Word counts: 5109

ACCEPTED MANUSCRIPT

## Abstract

Congenital bladder neck obstruction (or lower urinary tract obstruction [LUTO]) describes a heterogeneous group of congenital anomalies presenting with similar prenatal ultrasonographic findings of dilated posterior urethra, megacystis, hydronephrosis, oligohydramnios and often with associated renal dysplasia. Untreated LUTO has high rate of perinatal morbidity and mortality from associated pulmonary hypoplasia and early-onset renal failure in infancy. Ultrasonographic features and prospective fetal urinalysis may help in predicting the overall prognosis of congenital LUTO. Currently, fetal vesicoamniotic shunt (of various designs), and fetal cystoscopy and fulguration of the obstruction are potential prenatal interventions. Retrospective and prospective cohort studies and a relatively small randomized controlled trial have demonstrated these treatments may possibly improve perinatal survival. Despite this, concerns remain as to the high rates of renal impairment observed in paediatric survivors. A clinical prospective scoring / staging system may improve prenatal diagnostic criteria and case selection for fetal therapy.

Keywords

Congenital abnormalities, Fetal therapy, Prenatal ultrasonography, Urinary  
bladder neck obstruction

ACCEPTED MANUSCRIPT

**I) Introduction.**

The use of prenatal ultrasonography in routine pregnancy screening allows detection of fetal anomalies. Congenital renal and urinary tract anomaly constitutes approximately 21% of all congenital abnormalities (1) with a reported incidence of 1:250-1,000 pregnancies (2). In the latest report of UK renal registry in 2015, obstructive uropathy was the second most common underlying aetiology (19%) leading to end stage renal failure under the age of 16 years (3). The condition of congenital bladder neck obstruction is associated with a perinatal mortality rate of up to 45% for untreated cases (4) with approximately 30% developing end stage renal failure requiring paediatric dialysis and renal transplantation before the age of 5 years (5). Overall, childhood survival has been reported as being lowest for the cohort of patients starting renal dialysis or requiring transplantation before two years of age (hazard ratio of 4.1) when compared to the 12–16 years age group (3). Due to the high associated fetal and perinatal mortality with associated long-term morbidity in survivors there is enthusiasm for in-utero intervention in an attempt to modify the natural pathogenesis of congenital obstructive uropathy. However, this

should ideally not just ameliorate fetal and neonatal morbidity, but also long term renal and systemic impairment.

## **II) Prevalence and pathology**

Congenital lower urinary tract obstruction (LUTO) describes a heterogeneous group of anatomical uropathies with pathology primarily affecting the bladder neck or urethra. Population-based studies from Regional Congenital Anomaly Registers in the UK estimate prevalence of congenital lower urinary tract obstruction (LUTO) at between 2.2-3.3 per 10,000 births (6, 7). From these epidemiological studies, it appears that posterior urethral valves are the most common underlying pathology in LUTO (63%) (6,7), followed by urethral atresia (or stenosis) (17% of cases) (7). The male fetus appears to be more commonly affected by these pathologies whilst the prenatal ultrasonographic feature in a female fetus is often associated with a more complex pathology (e.g. persistent cloaca or megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)).

Congenital LUTO may be associated with chromosomal (most common trisomy



13 and 18) and monogenic abnormalities especially if extra-urological anomaly is present. The risk of chromosomal abnormality is approximately 15% in fetuses with 'megacystis' noted on ultrasound (8); with highest rates with a measured fetal longitudinal bladder length of 7-15mm compared to those >15mm at 10-14 gestational weeks (23.6% versus 11.4%) (9). In addition, congenital bladder neck obstruction may be associated with submicroscopic chromosomal anomalies, pathologic copy number variants and genetic variants identified by microarray and genome sequencing (10). "Prune-Belly syndrome" is a relatively rare congenital anomaly sequence characterized by severe megacystis, hydronephrosis, deficient abdominal wall musculature and bilateral undescended testes (in males) (11). A high prevalence of non-urological anomalies (up to 70%) is noted and again 'prune belly syndrome' may be associated with chromosomal abnormalities and single gene abnormalities (ACTA2 gene modification) (12,13). MMIHS almost exclusively affects female fetuses and is characterized by prenatal ultrasound dilation of both the distal bowel and bladder, with a primary abnormality of the smooth musculature

(heterozygous ACTG2 gene missense variants are reported, with a mutation in the actin genes) (14). The prognosis of both prune belly syndrome and MMIHS are very poor.

### **III) Diagnosis of LUTO**

LUTO can be detected by late first and second trimester of the pregnancy by screening ultrasonography (15). Differentiation of obstructive and non-obstructive aetiologies (e.g. vesicoureteric reflux) on prenatal sonography is challenging as both having similar ultrasound appearances. Whilst challenging, there are emerging clinical algorithms that appear to aid prognostic case selection for consideration of fetal therapy (see below).

Enlarged fetal urinary bladder caused by obstruction can be detected by ultrasonography after 10 weeks of gestation when the fetus starts to produce urine (16). In the first trimester, megacystis is usually defined as longitudinal bladder diameter  $\geq 7\text{mm}$  (8). In a recently published retrospective series of 541

cases of megacystis from the Netherland there was an even more heterogenous description of underlying pathologies. A final diagnosis was made in 418 cases. Investigation indicated that 53% (222/418) were isolated LUTO, 33% (136/418) had genetic, chromosomal or structural anomalies (such as trisomy 13/18/21, Turner syndrome, 22q11 microdeletion, VACTERL syndrome, cloacal malformation, overgrowth syndrome, etc.), and 14% (60/418) were normal or having isolated urological abnormality (vesicoureteric reflux or duplex colleting system) (17). Therefore, megacystis is not always associated with LUTO and serial ultrasound examinations allow identification of those cases with “spontaneous resolution” of the visualized bladder enlargement with investigation allowing triage and selection of isolated cases of posterior urethral valves most amenable to prenatal intervention. The chance of spontaneous resolution depends on the longitudinal bladder length. With the length of 7-15mm at 10-14 gestational weeks, 90% fetuses with a normal karyotype will resolve before 20 gestational weeks, while regression is unlikely for bladder length >15mm (9, 18). Another national study from the Netherlands shows

spontaneous resolution is more likely when the longitudinal bladder length is <12mm for megacystis presented before 18 weeks of gestation (19). Associated ultrasonographic features of nuchal translucency >95th centile and umbilical cord cysts could be unfavourable factors for spontaneous regression of megacystitis, and suggest complex megacystis and urethral atresia respectively (20). The high spontaneous resolution rate without urological consequence in first trimester megacystis can be explained by the autonomic innervation of bladder and appearance of smooth muscle occurring after 13 weeks of gestation (21). Transient bladder distention in early pregnancy could be physiological as there is no contractile tissue within the bladder (9). Persistent megacystis from first trimester could represent LUTO.

In the second and third trimester, the obstruction at the level of bladder neck leads to the classical ultrasonographic features of proximal dilatation of fetal urethra, enlarged urinary bladder (megacystis) and hydronephrosis (bi- or unilateral) (15) (Figure 1). Oligohydramnios and renal dysplastic change (either

macro or microcystic change in the renal parenchyma) are common additional features, depending on the degree of obstruction. The definition of megacystis in second and third trimester becomes variable but failure to empty an enlarged fetal urinary bladder over a period of 45 minutes or longitudinal diameter (in millimeter) greater than gestational age in weeks plus twelve are often accepted criteria (8). Both non-obstructive uropathy and LUTO can present as megacystis in the second and third trimester (22). A 'keyhole sign' can be seen if obstruction is at the bladder neck causing dilatation of the posterior urethra (Figure 1). Previous studies found this ultrasonographic sign very specific to LUTO especially in a fetus with posterior urethral valves (23, 24). However, a retrospective study showed that it was only present in 51.6% of fetus with proven posterior urethral valve and could be seen in 34.8% of other non-obstructive pathologies including vesicoureteric reflux and primary megaureter (25). Another retrospective study also demonstrated poor specificity of 48% to LUTO (26). This false positive finding could be explained by the distension of the lower portion of the urinary bladder, rather than the posterior

urethra, due to detrusor instability and bladder - sphincter dysynergy (24).

Similarly, hydronephrosis may be present on prenatal ultrasonographic examination in 88% of LUTO and 79% of non-obstructive uropathy (26), and therefore cannot differentiate the underlying aetiology and could represent obstructive processes as well as those of severe renal reflux.

The performance of prenatal ultrasonography to identify LUTO remains unsatisfactory, even with combination of ultrasonographic signs of megacystis (24, 25), dilated posterior urethral valve (23, 24) thickened bladder wall (23-25), dilated ureters (24), oligohydramnios /anhydramnios (24, 25) and abnormal renal parenchyma (macrocytic and/microcytic change) (23, 24). The sensitivity was only around 51% and around one quarter of prenatal cases suspicious of LUTO were normal at birth or reclassified to other non-obstructive uropathies, of which vesicoureteric reflux was the commonest, after postnatal examination (6, 7). In the Netherlands, a “clinical scoring system” has been derived from a retrospective national cohort of 143 cases of suspected LUTO after 18 weeks of

gestation. These data have recorded the degree of bladder distension, bilateral ureteral diameters, amniotic fluid status (maximal deepest vertical pool depth), fetal sex and fetal gestational age of referral as a numerical score (Table 1). A score of 4 was given for bladder volume  $>35\text{cm}^3$ /urinary ascites, oligohydramnios/ anhydramnios, male fetus and referral before 28 gestational weeks respectively, and score of 1.3 for each millimeter of ureteral dilatation. A cut-off of  $>9.5$  was suggested to differentiate the genuine obstructive uropathy from non-obstructive cause with 78% sensitivity and 79% specificity (Figure 2) (26). The weakness of these data is the exclusion of pregnancies where parents opted for termination of pregnancy.

Other imaging modalities, such as magnetic resonance imaging (MRI) have demonstrated some promise as a diagnostic imaging tool (27). Prenatal MRI may be performed in female fetus to assess urogenital obstructive anomaly and give additional information on the presence of microcolon, dilated esophagus and absence of abdominal musculature to suggest megacystis-microcolon-intestinal hypoperistalsis syndrome (28, 29). Three-dimensional virtual fetal cystoscopy by

MRI may provide another mean of fetal urinary tract evaluation (30) by virtual visualization of the urethral lumen, distended bladder and hydroureter, therefore potentially suggesting the underlying etiology non-invasively. However, in-utero MRI was mostly done during the third trimester and therefore its role in prenatal diagnosis of LUTO in first and second trimester is uncertain, which should be further explored in view of its non-invasive nature.

#### **IV) Prognostic evaluation and selection for fetal therapy**

The prognosis of congenital LUTO depends on the underlying pathology, severity of the obstruction, chromosomal abnormality and other associated structural anomaly. Invasive prenatal diagnostic test should be performed for genetic evaluation (8-14). A Detailed structural scan should be performed. A fetus with isolated prenatally confirmed LUTO with early onset oligohydramnios yet with reversible fetal renal function would benefit most from fetal intervention.

##### **a) Prognosis by ultrasonography**

In a systemic review, performed by our group, that included 13 studies and 215



women with confirmed LUTO postnatally, the most predictive ultrasonographic parameters at diagnosis for postnatal renal function were: a) renal cortical appearance (renal parenchyma echogenicity or cystic change within the renal cortex), with sensitivity of 0.57 (95% CI 0.37–0.76) and specificity of 0.84 (95% CI 0.71–0.94), and b) the presence of oligohydramnios, with sensitivity of 0.63 (95% CI 0.51–0.74) and specificity of 0.76 (95% CI 0.65–0.85) (31). However, no consistent definition of oligohydramnios was present in many of the included studies with many reporting this subjectively. A retrospective study analyzing 51 boys born with posterior urethral valve, using amniotic fluid of less than 5cm or the fifth centile to define oligohydramnios, gave a positive likelihood ratio of 17.0 (95% CI 2.4-122) to predict postnatal renal impairment (32). Renal cortical changes likely represent an irreversible in-utero renal damage, which leads to decrease fetal urinary output causing oligohydramnios. On the other hand, being a severe end of LUTO spectrum, oligohydramnios could also be due to complete blockage at bladder neck before the development of in-utero renal failure. Therefore, oligohydramnios could not be used alone to guide clinical

management because it could not differentiate the women with fetus in early stage of congenital LUTO who may benefit from intrauterine treatment to salvage the fetal renal function. Moreover, normal amniotic fluid at presentation could not guarantee normal postnatal renal function and 32% required renal replacement therapy after delivery (33).

Fetal bladder-refilling time has been purposed to assess the cortical renal function prospectively (34). Using the percentage of fetal bladder refilling ( $\text{fetal bladder volume 48 hours after vesicocentesis} - \text{fetal bladder volume before vesicocentesis} / (\text{fetal bladder volume before vesicocentesis}) \times 100$ ), a cut of  $<27\%$  could predict the residual renal function and the chance of progression to in-utero renal failure with 80% sensitivity and 75% specificity. In this cohort, eight fetuses developed in-utero renal failure, including four fetuses receiving fetal therapy with favorable urinary biochemistry, six died within first 24 hours of life and the two survivors required dialysis within the first week of life (34). Combining the gestational onset of oligohydramnios and fetal bladder volume,

Fontanella et al. stratified LUTO into mild (normal amniotic fluid at 26 weeks), moderate (bladder volume  $<5.4\text{cm}^3$  and normal amniotic fluid at 20 weeks) and severe (bladder volume  $\geq 5.4\text{cm}^3$  or oligohydramnios before 20 weeks) forms; the risk of perinatal mortality and postnatal renal dysfunction were 9% and 11% in mild; 26% and 31% in moderate; and 55% and 44% in severe cases respectively (35).

#### **b) Prognosis by fetal urinalysis**

Examination of fetal urine may provide valuable information on the degree of in-utero renal impairment and postnatal prognosis. Serial assessment by vesicocentesis every 48 hours is recommended, as again this in theory assesses the prospective ability of the kidney to produce and concentrate urine (36).

Theoretically, the first urine sample obtained by vesicocentesis represents the urinary stasis for prolonged period of time and the second urinary sample could mean the chronic urinary collection from upper urinary tract. The third urine sample should be fresh urine excreted by fetal kidney and truly reflect the

in-utero renal function (36). Fetus with salvageable renal function should demonstrate decreasing urine values and the third urine sample fall below the threshold value (<100mg/dl for sodium, <90mg/dl for chloride, < 200mOsm/L for osmolality, < 8 mg/dl for calcium, and < 20mg/dl for total protein,  $\beta$ -2 microglobulin <6mg/L) (36, 37). Unfavorable first sample could improve with sequential analysis (36). Therefore, using the first urine sample for clinical management may misclassify the in-utero renal function.

A systematic review, including 23 studies and 572 women with prenatal ultrasonographic evidence of LUTO, evaluated the use of urinary analyte to predict postnatal renal function (38). The two most useful urinary analytes were noted to be urinary calcium >95th centile for gestation (likelihood ratio positive 6.65; 95% CI 0.23–190.96; likelihood ratio negative 0.19; 95% CI 0.05–0.74) and sodium >95th centile for gestation (likelihood ratio positive 4.46; 95% CI 1.71–11.6; likelihood ratio negative 0.39; 95% CI 0.17–0.88). However, there was massive heterogeneity noted between studies in the review and in many cases

the cohort studies were small and retrospective. Therefore, none of the fetal urine analytes investigated yielded sufficient clinically significant accuracy to predict postnatal renal dysfunction. Furthermore, not all included studies were using serial vesicocentesis for assessment and fetuses with presumed LUTO were included, which mean some fetuses may turn out to have non-obstructive uropathy. New urinary peptide might help to predict the chance of postnatal renal impairment by higher sensitivity and specificity than traditional fetal urinalysis (39), which requires further validation.

**c) Selection of suitable candidates for fetal therapy – Combination of prognostic factors and a staging system**

The aim of fetal therapy is to prevent the complications from congenital LUTO, which are pulmonary hypoplasia leading to neonatal mortality, bladder dysfunction and development of postnatal renal failure requiring renal replacement therapy after birth. Detailed counseling of the parents before fetal therapy is crucial to meet reasonable expectations. For fetus with no evidence of

fetal renal failure, the objective is to preserve renal function in-utero, and prevent mortality and postnatal renal failure. For fetus with features of in-utero irreversible renal dysfunction, the role of fetal therapy is controversial, as the infant would require long-term dialysis or renal transplantation after birth and termination of pregnancy may be an option. However, as discussed, it remains challenging to estimate the fetal renal function. Since there is no significant association between ultrasonographic fetal renal appearance and urine biochemistry (40) and they may play an independent role in predicting postnatal renal function, prognostic evaluation should therefore be based on combination of different parameters from prenatal ultrasonography and fetal urinalysis. A staging system is proposed to guide the clinical management of congenital LUTO (Table 2) (41-43). A single centre retrospective study using this staging system showed good prognosis in five stage I disease with 100% survival and no end stage renal failure at 2 years (43). The survival and end stage renal failure rate at two years were 86% and 18% in stage II disease and 43% and 100% in stage III disease respectively. All fourteen women with stage II disease and three out of

seven women with stage III disease received fetal intervention. A significant limitation of this study was that postnatal diagnosis was not available and there were no control group in stage 2 and stage 3 diseases. This staging system is good in term of using combination of different prenatal parameters of serial assessment and offering suggestion for clinical management. The main limitation is that it does not incorporate the underlying primary pathology, which would affect the outcome ultimately. Adjustment in this staging system with the previous mentioned scoring system (26), MRI (27-30) and urinary peptide (39) assessment may be necessary in future and prospective evaluation with a control group would be meaningful.

## **V) Fetal intervention**

### **a) Vesicoamniotic shunting**

The placement of a vesicoamniotic shunt was initially described in the 1980s by Charles Rodeck theoretically, allowing free fetal urinary drainage from the urinary bladder (obstructed at the bladder neck) in order to relieve the pressure within the urinary system to prophylactically protect the kidneys against renal

damage. In addition, the placement of this “fetal suprapubic catheter” would restore normal amniotic fluid preventing pulmonary hypoplasia. It is a minimally invasive procedure, which involves ultrasonography-guided insertion of double pigtail catheter (usually a Rocket™ shunt) into the fetal urinary bladder (proximal end) and the amniotic cavity (distal end). This is usually performed with maternal sedation and with local anesthesia (Figure 2). A 16-gauge Rocket™ introducer needle is passed through the maternal abdomen, uterus and amniotic cavity under continuous real time ultrasound. The fetal abdominal wall and urinary bladder are then punctured using this trocar. The double pigtail catheter (Rocket™) is deployed with the distal end in the fetal urinary bladder and the proximal end is deployed in the amniotic space. Amnioinfusion of warmed (20°C) Physiological/ Hartmann’s solution may be necessary in case of anhydramnios to facilitate the procedure and to create an echolucent ‘operative window’. There are now several designs of pigtail catheters and each may have different success rates.



The only randomized controlled trial to evaluate the use of vesicoamniotic shunt versus conservative management was the Percutaneous vesicoamniotic shunting versus conservative management for Lower Urinary Tract Obstruction (PLUTO) trial (44). Women, who were pregnant with a male fetus showing ultrasonographic features of LUTO (visualization of enlarged bladder, dilated proximal urethra, presence of hydronephrosis and cystic parenchymal renal disease), were randomized to receive either percutaneous vesicoamniotic shunt or conservative management. Unfortunately, with a planned sample size of 150, the trial was prematurely stopped after recruiting 31 women due to poor recruitment rate. Clinicians would choose to use either a Rocket or Harrison shunt. In the analysis upon actual treatment received, 15 women received vesicoamniotic shunt and 16 women were managed conservatively, there were 11 and 13 live born, two and ten neonatal death within 28 days respectively. All neonatal deaths were secondary to complication of pulmonary hypoplasia. A statistically significant effect of vesicoamniotic shunting over conservative management was found on perinatal survival <28 days (RR 3.20; 95% CI 1.06–

9.62;  $P = 0.03$ ) in actual-treatment-received analysis. Renal impairment was noted in majority of the survivors in the vesicoamniotic shunt group. Complications were common and seen in six fetuses (40%) resulting in one miscarriage and three termination of pregnancy due to guarded prognosis. The complications were spontaneous rupture of membranes, and shunt dislodgement or blockage. Furthermore, the long-term outlook of the survivors in the intervention group was not promising. Only seven were alive at two years of age, and five of them had renal impairment. Within the PLUTO RCT, there were no prognostic indicators for fetal therapy. Instead, a pragmatic clinical approach was used based on clinician equipoise. A parallel non-randomized registry included a variable case mix and thus logistic regression analysis was able to identify that gestation at diagnosis  $< 24$  weeks and liquor volume were poor prognostic indicators.

A systematic review of nine studies, including the PLUTO RCT, involving 246 fetuses compared 112 vesicoamniotic shunt with 134 conservative management

(45). Cases of termination and chromosomal anomalies were excluded. Congenital LUTO was defined by presence of enlarged fetal bladder and bilateral hydronephrosis. Although a better perinatal survival was observed after vesicoamniotic shunt insertion, there was no difference in postnatal survival at 6-12 months and at 2 years. The postnatal renal function was not different in the two groups. Confirmation of LUTO was not specified in some studies. Again, proper prognostic prioritization before subject recruitment was not formally done in most studies. There was only one randomized controlled trial and therefore possible selection bias.

The urinary bladder function was not evaluated in most of the interventional studies using vesicoamniotic shunt. A long term follow up study, at mean age of 54.3 months after fetal vesicoamniotic shunt insertion, reported 75% bladder augmentation in survivors of posterior urethral valve and 28.5% of total survivors needed intermittent catheterization (46). Normal bladder filling and emptying cycle could be essential to perverse the urinary bladder compliance. In

animal model, the abolishment this cycle after putting a vesicoamniotic shunt in lamb without LUTO can also create a fibrotic bladder with poor compliance after delivery (47). Putting a low-pressure valved vesicoamniotic shunt could theoretically preserve bladder compliance with less associated muscle fibrosis (47) but no human study has so far been described using this type of shunt.

#### **b) Fetal cystoscopy**

Postnatally, posterior urethral valves are treated with cystoscopic fulguration thus the use of the same procedure prenatally may have some advantages. The development of <2mm endoscope allows fetal cystoscopy to be performed in early pregnancy (Figure 4). The major advantages of fetal cystoscopy over vesicoamniotic shunt are direct visualization of the bladder neck providing diagnostic identification of the underlying pathology and thus specific therapeutic treatment where available (48). The diagnostic information obtained may again aid prognostic counseling to the women. In addition, relieving the obstruction during fetal life could allow a more 'physiological' drainage of the

urine and thus normal bladder muscle development.

Fetal cystoscopy can be performed under regional anesthesia or maternal sedation with local analgesia (48-50). Fetal sedation is achieved by intraumbilical or fetal intramuscular injection to the arm/leg of fentanyl and pancuronium under ultrasonographic guidance, using a 22-gauge needle. A 2.2-3.3mm curved sheath is inserted through the maternal abdomen, uterus, amniotic space and fetal urinary bladder under ultrasonographic guidance (Figure 3). The fetoscope is advanced toward the bladder neck with a dilated posterior urethra. Transurethral stenting of urethral stenosis or ablation of the posterior urethral valve can be performed. Clearance of obstruction can be confirmed by water injection through the cystoscopy and observing the flow along the urethra under power Doppler study. It is a technically demanding procedure and often visualization of the proximal urethra is difficult or impossible due to the angle of the bladder axis to the urethral axis. There is a reported high risk of preterm pre-labour rupture of membranes and this is a

significant complication (23%) (50). In addition, cohort studies have recorded complications such as 'false tract' formation and iatrogenic urological fistula formation after ablation (around 10%) (49). A curve trocar and insertion at the upper fetal bladder (different from vesicoamniotic shunt) is necessary to visualize the fetal bladder neck, which may also lead to umbilical vein laceration (50).

A systematic review of the cohort studies of fetal cystoscopy for the investigation and treatment of LUTO identified four papers with a total of 63 subjects (48). Fetal cystoscopy altered the prospective prenatal diagnosis in 25–36% of cases and the sensitivity was 83-100% for diagnosing posterior urethral valve and 100% for urethral atresia. Improvement of perinatal survival was observed in fetal cystoscopy group compared with no intervention (Odd ratio 20.51; 95% CI 3.87–108.69) but not when compared with vesicoamniotic shunt (Odd ratio 1.49; 95% CI 0.13–16.97). Overall, a small number of studies, mainly retrospective with small sample size and a lack of randomized controlled trial hinder these

conclusions.

A retrospective cohort study of 48 cases of confirmed LUTO with normal karyotype showed the risk of fetal demise was 4.2% after fetal cystoscopy and neonatal mortality rate was 22.9% (50). The survival rate and infants with normal function were 37.5% and 77.8% at one year of age, and 34.8% and 75% at two years of age respectively. Outcomes of urethral atresia and stenosis were extremely poor, with majority of women opted for termination of pregnancy (72%), four neonatal death (22%) and only one survivor whom received transurethral stenting for urethral stenosis. For fetus with posterior urethra valve, there was 20% recurrence of LUTO in which half required additional fetal therapy, 13.3% risk of urological fistulas formation and 3.3% risk of fetal umbilical vein laceration. The survival rate and infant with normal renal function at one year and two years of age were around 55% and 75% respectively.

### **c) Fetal cystoscopy versus vesicoamniotic shunt**

There is no randomized controlled trial to allow head to head comparison between these two fetal interventions. Ruano *et al.* performed a retrospective analysis of 111 male fetuses with prenatal presumed LUTO (51). 34 fetuses received fetal cystoscopy, 16 fetuses had vesicoamniotic shunt and 61 controls had no fetal therapy. Fetal intervention, either by fetal cystoscopy and vesicoamniotic shunt, was significantly associated with better survival when compared to control group (adjusted relative risk (ARR), 1.86 (95% CI, 1.01–3.42; P=0.048) and ARR, 1.73 (95% CI, 1.01–3.08; P=0.04) respectively). A trend of favoring normal renal function was observed in the fetal cystoscopy group (ARR, 1.73 (95% CI, 0.97–3.08; P=0.06)) but not in the vesicoamniotic shunt group. For fetus with posterior urethral valve confirmed after delivery, fetal cystoscopy improved renal function at 6-month (ARR, 2.66 (95% CI, 1.25–5.70; P=0.01)), while this effect was not seen in the vesicoamniotic shunting group (ARR, 1.03 (95% CI, 0.49–2.17, P=0.93)). Shunt obstruction or migration occurred in 31.3% in vesicoamniotic group and urological fistula happened in 8.8% of fetal cystoscopy group. A randomized controlled trial is proposed to compare both



interventions in LUTO (NCT01552824).

#### **d) Minimizing complications**

The type of shunt may affect the chance of shunt dislodgement. The Harrison Fetal Bladder Stent was associated with a higher dislodgement rate than the Rocket® KCH™ Fetal Bladder Catheter (78% versus 30%) (52). Choosing the optimal instrument and energy may prevent urological fistula formation during fetal cystoscopy (49). A true curved sheath allows adequate access to the fetal bladder neck and subsequent correct angle to apply laser to the posterior urethral valve. The use of lowest effective energy during treatment and fetal anesthesia can decrease the chance of inadvertent peripheral tissue damage. Similar to other fetal intervention (53), operators' experience could increase the chance of success and decrease complication (50).

#### **VI) Clinical approach to LUTO – from screening to management**

A suggested clinical approach to LUTO first detected during first and second

trimester of pregnancy is presented in Figure 5. Conservative management with serial ultrasonographic monitoring is recommended for LUTO with normal amniotic fluid volume and renal appearance. Option of termination of pregnancy may be discussed if there is sign of in-utero renal failure, especially before 24 weeks of gestation, by the presence of oligohydramnios/ anhydramnios and renal dysplastic feature, which indicates high chance of pulmonary hypoplasia and postnatal renal failure.

LUTO with oligohydramnios and no obvious ultrasonographic feature of irreversible renal damage may benefit from fetal intervention and requires further evaluation by detailed structural scan, invasive test for genetic study and serial fetal urinalysis in order to determine the likelihood of a true obstructive uropathy and estimate the remaining in-utero renal function. Fetal therapy could be discussed in those with signs indicative of a favorable prognosis to prevent complications from LUTO (stage 2 +/- stage 3). In fetus with in-utero renal failure (stage 4), vesicocentesis and fetal cystoscopy cannot restore amniotic fluid

volume (as decrease fetal urine output) and renal damage has already occurred. Therefore, vesicoamniotic shunt and fetal cystoscopy are not recommended. The management is complex and controversial if the parents consider continuation of the pregnancy. Although repeated amnioinfusion may be a treatment option aiming to prevent pulmonary hypoplasia (54), concerns remain on the potential procedural related risk of maternal infection, preterm prelabour rupture of membranes and preterm delivery, which further worsen the maternal and neonatal prognosis (55, 56). In addition, significant neonatal morbidity and mortality is expected, even after repeated amnioinfusion, due to perinatal renal failure (56). Furthermore, the optimal gestational age to initiate, frequency of amnioinfusion, short-term and long-term morbidities and quality of life after treatment are not clear (55). The efficacy to prevent hypoplasia is also not known. However, the rapid improvement in the management of neonatal renal failure improve the outlook of these babies, which may make pulmonary palliation in-utero and neonatal renal replacement therapy (dialysis or transplantation) an feasible option in future (56). Therefore, detailed counseling and proper

evaluation under research setting is required if active intervention is sought.

LUTO presenting in the third trimester is uncommon due to the widely available prenatal screening ultrasonography, which permits early detection of LUTO. First presentation at this gestation may represent a milder disease with incomplete/transient obstruction (likely normal in-utero renal function) or severe LUTO when early screening ultrasonography is not available (likely damaged fetal kidneys). Fetal therapy is usually not indicated in both situations.

If there is a need to consider fetal intervention for LUTO in the third trimester especially after 34 weeks of gestation, one needs to balance the risk of preterm delivery by fetal therapy, which may add extra burden, and on-going renal injury by expectant management. It seems reasonable to consider delivery at term if there is a concern of possible on-going renal damage. Earlier elective delivery to prevent renal complication is controversial.

## VII) Summary

Congenital LUTO can be detected by prenatal first and second trimester screening ultrasonography. It can lead to significant mortality and long-term morbidity, which may be ameliorated by fetal therapy. The success of fetal therapy depends heavily on proper selection of suitable candidates, which is currently hindered by the difficulty in prenatal identification of underlying etiology (obstructive or non-obstructive uropathy) and the lack of reliable prenatal markers to predict the in-utero course and subsequent renal impairment after birth. New advances in clinical scoring system (26), in-utero renal function assessment by fetal bladder refilling (34) and fetal urinary peptide assessment (39), non-invasive evaluation by MRI (27-30) and staging system (41-43) would definitely refine the management of congenital suspected LUTO. Vesicoamniotic shunt and fetal cystoscopy are the main fetal therapies for LUTO. These interventions could improve neonatal survival rate but, unfortunately, have failed to demonstrate long-term renal benefits. Fetal cystoscopy may be more appealing in view of the advantages over vesicoamniotic shunt, but is technically challenging. A well-designed and coordinated randomized controlled

trial is certainly needed to reveal the role of fetal therapy in LUTO.

### **Conflict of interest statement**

The authors have stated explicitly that there are no conflicts of interest in connection with this article. R. K. M. and M. D. K. were funded by a by the UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) grant from 2008-2013 to study congenital bladder neck obstruction and fetal intervention to treat this anomaly.

**Practice points**

- Congenital non-obstructive uropathy can share similar prenatal ultrasonographic characteristic with obstructive uropathy.
- Prognostic estimation is essential before fetal therapy
- Fetal intervention can improve perinatal survival but survivors still have a high rate of renal impairment.

**Research agenda**

- Non-invasive modality for prenatal diagnosis of congenital lower urinary tract obstruction
- Use of magnetic resonance imaging, urinary biomarkers and other new ultrasonographic markers to estimate in-utero renal function
- Trials, using a staging system, to evaluate fetal therapy in congenital lower urinary tract obstruction
- Long term outcomes of survivors after fetal intervention

## Reference

1. Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. *Am J Obstet Gynecol.* 1999;181:446-54.
2. Lewis MA. Demography of renal disease in childhood. *Semin Fetal Neonatal Med.* 200;13:118-24.
3. Hamilton AJ, Braddon F, Casula A, Lewis M, Mallett T, Marks SD, et al. UK Renal Registry 19th Annual Report: Chapter 4 Demography of the UK Paediatric Renal Replacement Therapy Population in 2015. *Nephron.* 2017;137:103-116.
4. Freedman AL, Johnson MP, Gonzalez R. Fetal therapy for obstructive uropathy: past, present, future? *Pediatr Nephrol.* 2000;14:167-76.
5. Parkhouse HF, Barratt TM, Dillon MJ, Duffy PG, Fay J, Ransley PG, et al. Long-term outcome of boys with posterior urethral valves. *Br J Urol.* 1988;62:59-62.
6. Anumba DO, Scott JE, Plant ND, Robson SC. Diagnosis and outcome of fetal



- lower urinary tract obstruction in the northern region of England. *Prenat Diagn.* 2005;25:7-13.
7. \*Malin G, Tonks AM, Morris RK, Gardosi J, Kilby MD. Congenital lower urinary tract obstruction: a population-based epidemiological study. *BJOG.* 2012;119:1455-64.
  8. Taghavi K, Sharpe C, Stringer MD. Fetal megacystis: A systematic review. *J Pediatr Urol.* 2017;13:7-15.
  9. Liao AW, Sebire NJ, Geerts L, Cicero S, Nicolaides KH. Megacystis at 10-14 weeks of gestation: chromosomal defects and outcome according to bladder length. *Ultrasound Obstet Gynecol.* 2003;21:338-41.
  10. Boghossian NS, Sicko RJ, Kay DM, Rigler SL, Caggana M, Tsai MY, et al. Rare copy number variants implicated in posterior urethral valves. *Am J Med Genet A.* 2016;170:622-33.
  11. Tonni G, Ida V, Alessandro V, Bonasoni MP. Prune-belly syndrome: case series and review of the literature regarding early prenatal diagnosis, epidemiology, genetic factors, treatment, and prognosis. *Fetal Pediatr Pathol.*

2013;31:13-24.

12. Richer J, Milewicz DM, Gow R, de Nanassy J, Maharajh G, Miller E, et al. R179H mutation in ACTA2 expanding the phenotype to include prune-belly sequence and skin manifestations. *Am J Med Genet A*. 2012;158A:664-8.
13. Boghossian NS, Sicko RJ, Giannakou A, Dimopoulos A, Caggana M, Tsai MY, et al. Rare copy number variants identified in prune belly syndrome. *Eur J Med Genet*. 2018;61:145-151.
14. De Sousa J, Upadhyay V, Stone P. Megacystis Microcolon Intestinal Hypoperistalsis Syndrome: Case Reports and Discussion of the Literature. *Fetal Diagn Ther*. 2016;39:152-7.
15. Robyr R, Benachi A, Daikha-Dahmane F, Martinovich J, Dumez Y, Ville Y. Correlation between ultrasound and anatomical findings in fetuses with lower urinary tract obstruction in the first half of pregnancy. *Ultrasound Obstet Gynecol*. 2005;25:478-82.
16. McHugo J, Whittle M. Enlarged fetal bladders: aetiology, management and outcome. *Prenat Diagn*. 2001;21:958-63.

17. Fontanella F, Maggio L, Verheij JBG, Duin LK, Adama van Scheltema PN, Cohen-Overbeek TE, et al. Fetal megacystis: a lot more than LUTO. *Ultrasound Obstet Gynecol.* 2018 Jul 24.
18. Kagan KO, Staboulidou I, Syngelaki A, Cruz J, Nicolaides KH. The 11-13-week scan: diagnosis and outcome of holoprosencephaly, exomphalos and megacystis. *Ultrasound Obstet Gynecol.* 2010;36:10-4.
19. Fontanella F, Duin L, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, et al. Fetal megacystis: prediction of spontaneous resolution and outcome. *Ultrasound Obstet Gynecol.* 2017;50:458-463.
20. Fontanella F, Duin L, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, et al. Antenatal Workup of Early Megacystis and Selection of Candidates for Fetal Therapy. *Fetal Diagn Ther.* 2018 May 17:1-7.
21. Newman J, Antonakopoulos GN. The fine structure of the human fetal urinary bladder. Development and maturation. A light, transmission and scanning electron microscopic study. *J Anat.* 1989 Oct;166:135-50.
22. Fievet L, Faure A, Coze S, Harper L, Panait N, Braunstein D, et al. Fetal

megacystis: etiologies, management, and outcome according to the trimester.

Urology. 2014;84:185-90.

23. Montemarano H, Bulas DI, Rushton HG, Selby D. Bladder distention and pyelectasis in the male fetus: causes, comparisons, and contrasts. J Ultrasound Med. 1998;17:743-9.
24. Chitrit Y, Bourdon M, Korb D, Grapin-Dagorno C, Joinau-Zoulovits F, Vuillard E, et al. Posterior urethral valves and vesicoureteral reflux: can prenatal ultrasonography distinguish between these two conditions in male fetuses? Prenat Diagn. 2016;36:831-7.
25. Bernardes LS, Aksnes G, Saada J, Masse V, Elie C, Dumez Y, et al. Keyhole sign: how specific is it for the diagnosis of posterior urethral valves? Ultrasound Obstet Gynecol. 2009;34:419-23.
26. \*Fontanella F, Duin LK, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, et al. Prenatal diagnosis of LUTO: how to improve diagnostic accuracy. Ultrasound Obstet Gynecol. 2017 Dec 20.
27. Abdelazim IA, Abdelrazak KM, Ramy AR, Mounib AM. Complementary roles

- of prenatal sonography and magnetic resonance imaging in diagnosis of fetal renal anomalies. *Aust N Z J Obstet Gynaecol.* 2010;50:237-41.
28. Capito C, Belarbi N, Paye Jaouen A, Leger J, Carel JC, Oury JF, et al. Prenatal pelvic MRI: additional clues for assessment of urogenital obstructive anomalies. *J Pediatr Urol.* 2014;10:162-6.
29. Millischer AE, Grevent D, Rousseau V, O'Gorman N, Sonigo P, Bessieres B, et al. Fetal MRI compared with ultrasound for the diagnosis of obstructive genital malformations. *Prenat Diagn.* 2017;37:1138-1145.
30. Werner H, Lopes J, Ribeiro G, Jésus NR, Santos GR, Alexandria HAF, et al. Three-dimensional virtual cystoscopy: Noninvasive approach for the assessment of urinary tract in fetuses with lower urinary tract obstruction. *Prenat Diagn.* 2017;37:1350-1352.
31. \*Morris RK, Malin GL, Khan KS, Kilby MD. Antenatal ultrasound to predict postnatal renal function in congenital lower urinary tract obstruction: systematic review of test accuracy. *BJOG.* 2009;116:1290-9.
32. Harper L, Waubant A, Vignes J, Amat S, Dobremez E, Lefevre Y, et al. Can

- quantity of amniotic fluid reliably predict postnatal renal function in boys with posterior urethral valves: a decision curve analysis. *Prenat Diagn.* 2017;37:931-934
33. Johnson MP, Danzer E, Koh J, Polzin W, Harman C, O'Shaughnessy R, et al. Natural History of Fetal Lower Urinary Tract Obstruction with Normal Amniotic Fluid Volume at Initial Diagnosis. *Fetal Diagn Ther.* 2017 Jul 13.
34. \*Ruano R, Safdar A, Au J, Koh CJ, Gargollo P, Shamshirsaz AA, et al. Defining and predicting 'intrauterine fetal renal failure' in congenital lower urinary tract obstruction. *Pediatr Nephrol.* 2016;31:605-12.
35. Fontanella F, Adama van Scheltema PN, Duin L, Cohen-Overbeek TE, Pajkrt E, Bekker MN, et al. Antenatal staging of congenital lower urinary tract obstruction. *Ultrasound Obstet Gynecol.* 2018 Jul 5.
36. Johnson MP, Corsi P, Bradfield W, Hume RF, Smith C, Flake AW, et al. Sequential urinalysis improves evaluation of fetal renal function in obstructive uropathy. *Am J Obstet Gynecol.* 1995;173:59-65.
37. Walsh DS, Johnson MP. Fetal interventions for obstructive uropathy. *Semin*

- Perinatol. 1999;23:484-95.
38. \*Morris RK, Quinlan-Jones E, Kilby MD, Khan KS. Systematic review of accuracy of fetal urine analysis to predict poor postnatal renal function in cases of congenital urinary tract obstruction. *Prenat Diagn.* 2007;27:900-11.
39. Klein J, Lacroix C, Caubet C, Siwy J, Zürbig P, Dakna M, et al. Fetal urinary peptides to predict postnatal outcome of renal disease in fetuses with posterior urethral valves (PUV). *Sci Transl Med.* 2013;5:198ra106.
40. Nassr AA, Koh CK, Shamshirsaz AA, Espinoza J, Sangi-Haghpeykar H, Sharhan D, et al. Are ultrasound renal aspects associated with urinary biochemistry in fetuses with lower urinary tract obstruction? *Prenat Diagn.* 2016;36:1206-1210.
41. Ruano R, Sananes N, Wilson C, Au J, Koh CJ, Gargollo P, et al. Fetal lower urinary tract obstruction: proposal for standardized multidisciplinary prenatal management based on disease severity. *Ultrasound Obstet Gynecol.* 2016;48:476-482.
42. Ruano R, Dunn T, Braun MC, Angelo JR, Safdar A. Lower urinary tract

obstruction: fetal intervention based on prenatal staging. *Pediatr Nephrol.*

2017 Jul 21.

43. \*Farrugia MK, Braun MC, Peters CA, Ruano R, Herndon CD. Report on The Society for Fetal Urology panel discussion on the selection criteria and intervention for fetal bladder outlet obstruction. *J Pediatr Urol.* 2017;13:345-351.
44. \*Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Hemming K, Burke D, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet.* 2013;382:1496-506.
45. \*Nassr AA, Shazly SAM, Abdelmagied AM, Araujo Júnior E, Tonni G, Kilby MD, et al. Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2017;49:696-703.
46. Freedman AL, Johnson MP, Smith CA, Gonzalez R, Evans MI. Long-term outcome in children after antenatal intervention for obstructive uropathies.



- Lancet. 1999;354:374-7.
47. Pringle KC, Kitagawa H, Seki Y, Koike J, Zuccollo J. Development of an animal model to study congenital urinary obstruction. *Pediatr Surg Int.* 2013;29:1083-9.
  48. \*Morris RK, Ruano R, Kilby MD. Effectiveness of fetal cystoscopy as a diagnostic and therapeutic intervention for lower urinary tract obstruction: a systematic review. *Ultrasound Obstet Gynecol.* 2011;37:629-37.
  49. Sananes N, Favre R, Koh CJ, Zaloszyc A, Braun MC, Roth DR, et al. Urological fistulas after fetal cystoscopic laser ablation of posterior urethral valves: surgical technical aspects. *Ultrasound Obstet Gynecol.* 2015;45:183-9.
  50. Sananes N, Cruz-Martinez R, Favre R, Ordorica-Flores R, Moog R, Zaloszy A, et al. Two-year outcomes after diagnostic and therapeutic fetal cystoscopy for lower urinary tract obstruction. *Prenat Diagn.* 2016;36:297-303.
  51. Ruano R, Sananes N, Sangi-Haghpeykar H, Hernandez-Ruano S, Moog R, Becmeur F, et al. Fetal intervention for severe lower urinary tract obstruction: a multicenter case-control study comparing fetal cystoscopy

- with vesicoamniotic shunting. *Ultrasound Obstet Gynecol.* 2015;45:452-8.
52. Kurtz MP, Koh CJ, Jamail GA, Sangi-Haghpeykar H, Shamshirsaz AA, Espinoza J, et al. Factors associated with fetal shunt dislodgement in lower urinary tract obstruction. *Prenat Diagn.* 2016;36:720-5.
53. Diehl W, Diemert A, Grasso D, Sehner S, Wegscheider K, Hecher K. Fetoscopic laser coagulation in 1020 pregnancies with twin-twin transfusion syndrome demonstrates improvement in double-twin survival rate. *Ultrasound Obstet Gynecol.* 2017;50:728-735.
54. Haeri S, Simon DH, Pillutla K. Serial amnioinfusions for fetal pulmonary palliation in fetuses with renal failure. *J Matern Fetal Neonatal Med.* 2017;30:174-176.
55. Sugarman J, Anderson J, Baschat AA, Herrera Beutler J, Bienstock JL, Bunchman TE, et al. Ethical Considerations Concerning Amnioinfusions for Treating Fetal Bilateral Renal Agenesis. *Obstet Gynecol.* 2018;131:130-134.
56. Gimpel C, Avni FE, Bergmann C, Cetiner M, Habbig S, Haffner D, et al. Perinatal Diagnosis, Management, and Follow-up of Cystic Renal Diseases: A

Clinical Practice Recommendation With Systematic Literature Reviews.

JAMA Pediatr. 2018;172:74-86.

ACCEPTED MANUSCRIPT

Table 1. Clinical scoring system to predict congenital LUTO	
	Score
Severe megacystis (bladder volume >35cm <sup>3</sup> /urinary ascites)	4
Bilateral ureteral diameters	1.3 for each millimeter of ureteral dilatation
Oligohydramnios/ anhydramnios	4
Male fetus	4
Referral before 28th gestational weeks	4

Adapted from Fontanella F, Duin LK, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, Willekes C, Bax CJ, Gracchi V, Oepkes D, Bilardo CM. Prenatal diagnosis of LUTO: how to improve diagnostic accuracy. *Ultrasound Obstet Gynecol.* 2017 Dec 20.

	Stage I	Stage II	Stage III	Stage IV
Amniotic fluid	Normal	Oligohydramnios	Anhydramnios/ oligohydramnios	Anhydramnios
Fetal renal appearance on ultrasonography	Normal	Normal to echogenic	Echogenic, presence of renal cyst $\pm$ dysplasia Bladder refilling $>$ 27% 48 hours after vesicocentesis	Echogenic, presence of renal cyst and dysplasia Bladder refilling $\leq$ 27% 48 hours after vesicocentesis
Fetal urinalysis	Favourable (usually fetal analysis not indicated)	Favourable after sequential sampling	Unfavourable after sequential sampling	Unfavourable after sequential sampling
Interpretation	- Likely partial/transient obstruction - Low risk of pulmonary hypoplasia and in-utero renal failure	- Risk of pulmonary hypoplasia if oligohydramnios $<$ 24 weeks - Likely normal/reversible fetal renal function	- Risk of pulmonary hypoplasia if anhydramnios/oligohydramnios $<$ 24 weeks, - Possible in-utero renal failure	- Risk of pulmonary hypoplasia if anhydramnios/oligohydramnios $<$ 24 weeks - Likely in-utero renal failure
Risk and prognosis	Generally good prognosis	Risk of pulmonary hypoplasia and renal failure	Risk of neonatal death and renal failure	Guarded prognosis, high risk of early neonatal death
Management (Also see Figure 5)	One to two weekly monitoring	Vesicoamniotic shunt or fetal cystoscopy	Vesicoamniotic shunt or fetal cystoscopy	Option of termination of pregnancy ? Serial amnioinfusion
Rational of fetal	Not indicated	Prevent perinatal	Prevent perinatal	Controversial,

intervention		mortality and postnatal renal failure	mortality but may have postnatal renal impairment	expect renal failure at birth and mortality
--------------	--	---------------------------------------	---	---

Modified from Ruano R, Dunn T, Braun MC, Angelo JR, Safdar A. Lower urinary tract obstruction: fetal intervention based on prenatal staging. *Pediatr Nephrol.* 2017;32:1871-1878.

ACCEPTED MANUSCRIPT

Figure 1. Typical prenatal ultrasonographic findings of lower urinary tract obstruction. (a) A dilated proximal urethra, known as keyhole sign. (b) Enlarged fetal urinary bladder and hydronephrosis.

Kilby MD, Morris RK. Fetal therapy for the treatment of congenital bladder neck obstruction. *Nat Rev Urol.* 2014;11:412-9.

Figure 2. Receiver-operating curves for prenatal prediction of congenital lower urinary tract obstruction (clinical scoring —, classic triad ---)

Fontanella F, Duin LK, Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, Willekes C, Bax CJ, Gracchi V, Oepkes D, Bilardo CM. Prenatal diagnosis of LUTO: how to improve diagnostic accuracy. *Ultrasound Obstet Gynecol.* 2017 Dec 20.

Figure 3. Prenatal vesicoamniotic shunt placement.

(a) Schematic illustration of vesicoamniotic shunting. (b) Post-insertion ultrasonography, demonstrating correct placement of vesicoamniotic pigtail catheter with the proximal end in the bladder and the distal end in the amniotic cavity (arrows).

Adapted with permission from BMJ Publishing Group Limited. Morris, R. K. et al. Vesicoamniotic shunting for fetal lower urinary tract obstruction: an overview. *Arch. Dis. Child Fetal Neonatal Ed.* 92, F166–F168 (2007).

Figure 4. Visualization of the fetal bladder neck by fetal cystoscopy.

(a) An endoscope in a curved sheath was inserted through the maternal abdomen and uterus into the fetal bladder allowing direct visualization of the fetal bladder neck. (b) Cystoscopic view of a dilated posterior urethra.

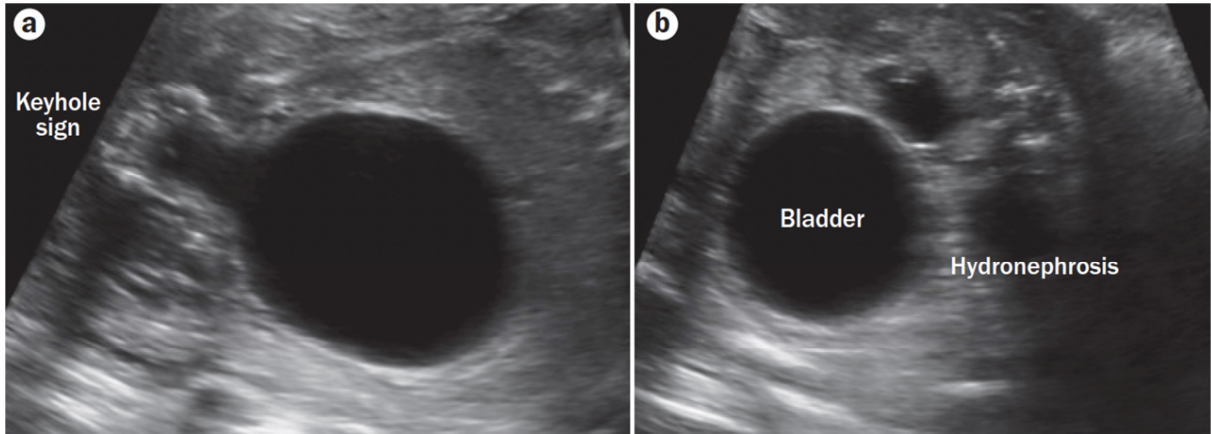
Abbreviations: LF, laser fibre; PUV, posterior urethral valve.

Permission obtained from Cambridge University Press © Kilby, M. D. et al. (eds) *Fetal Therapy: Scientific Basis and Critical Appraisal of Clinical Benefits* (2012). (Provided by Dr Ruano Rodrigo)

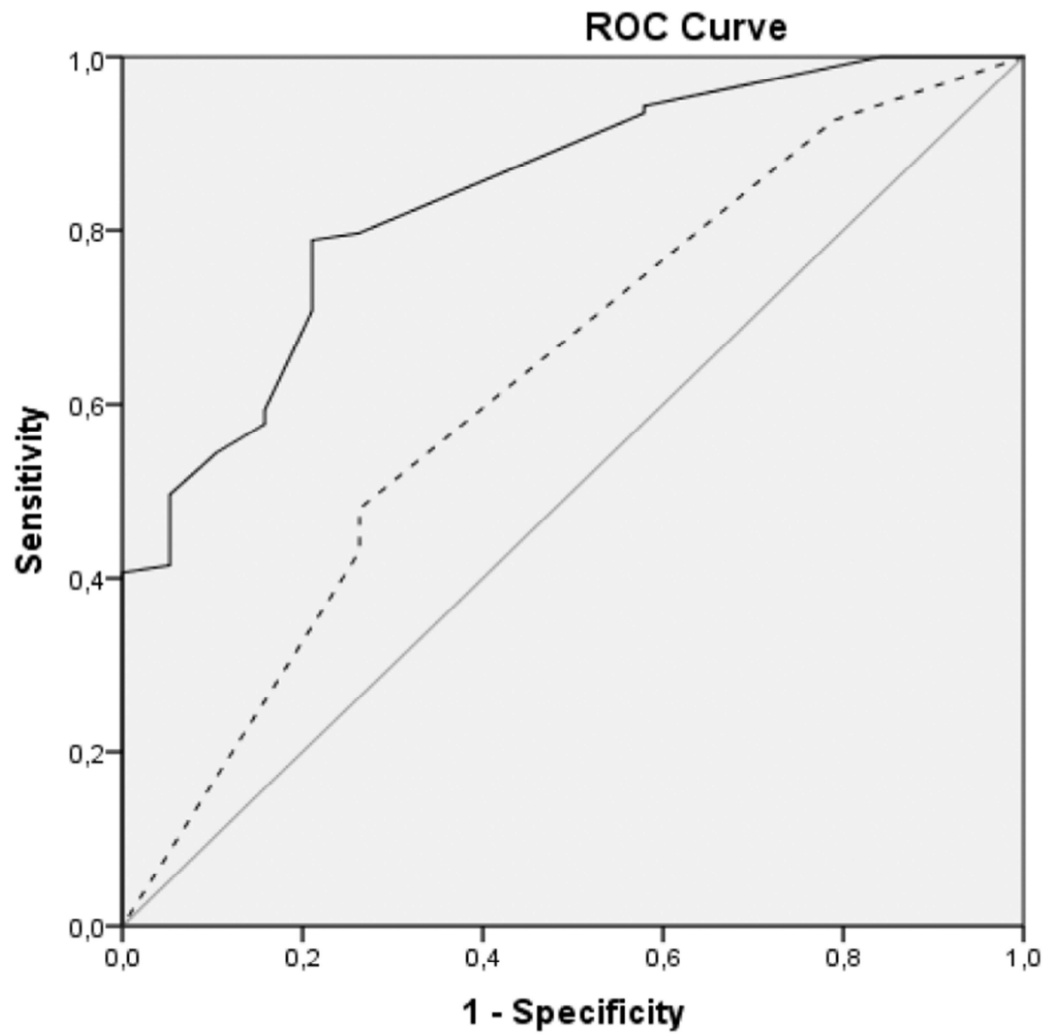
Figure 5. Clinical approach to LUTO – from screening to treatment

ACCEPTED MANUSCRIPT

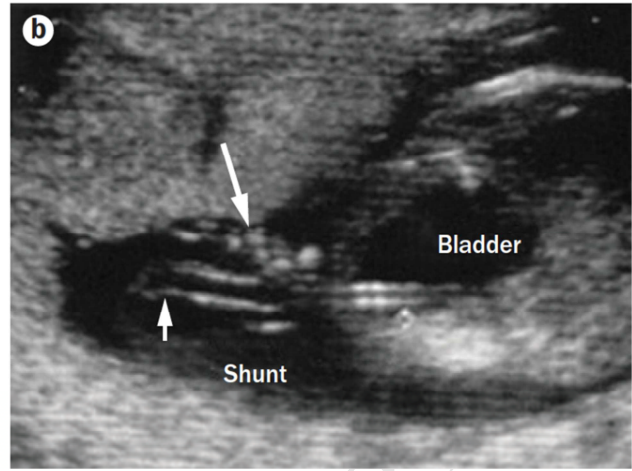
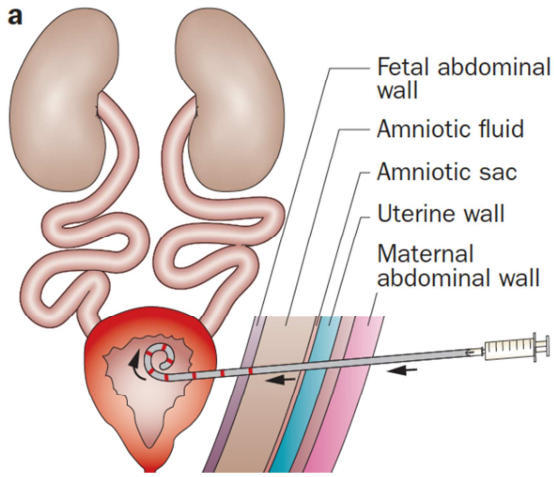




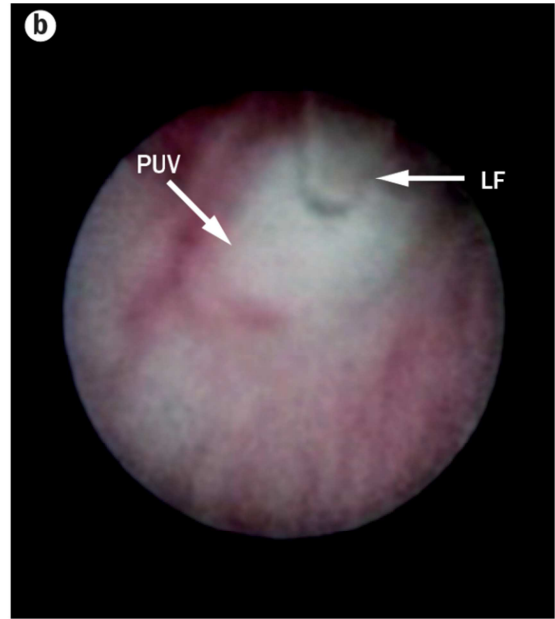
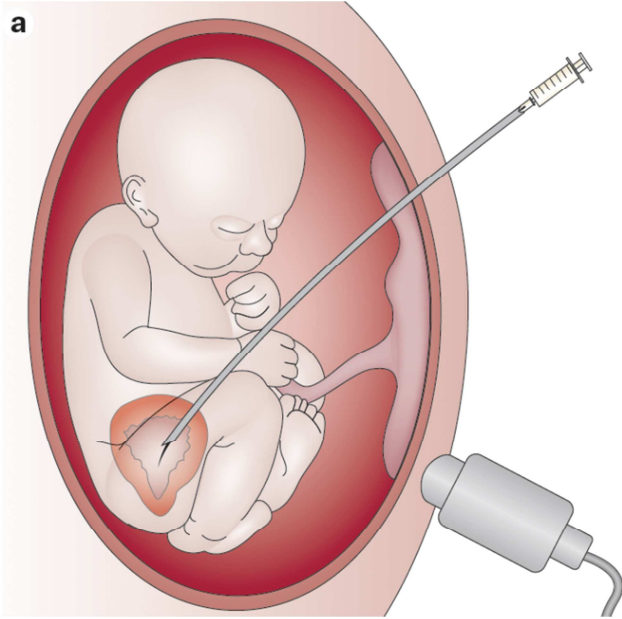
ACCEPTED MANUSCRIPT



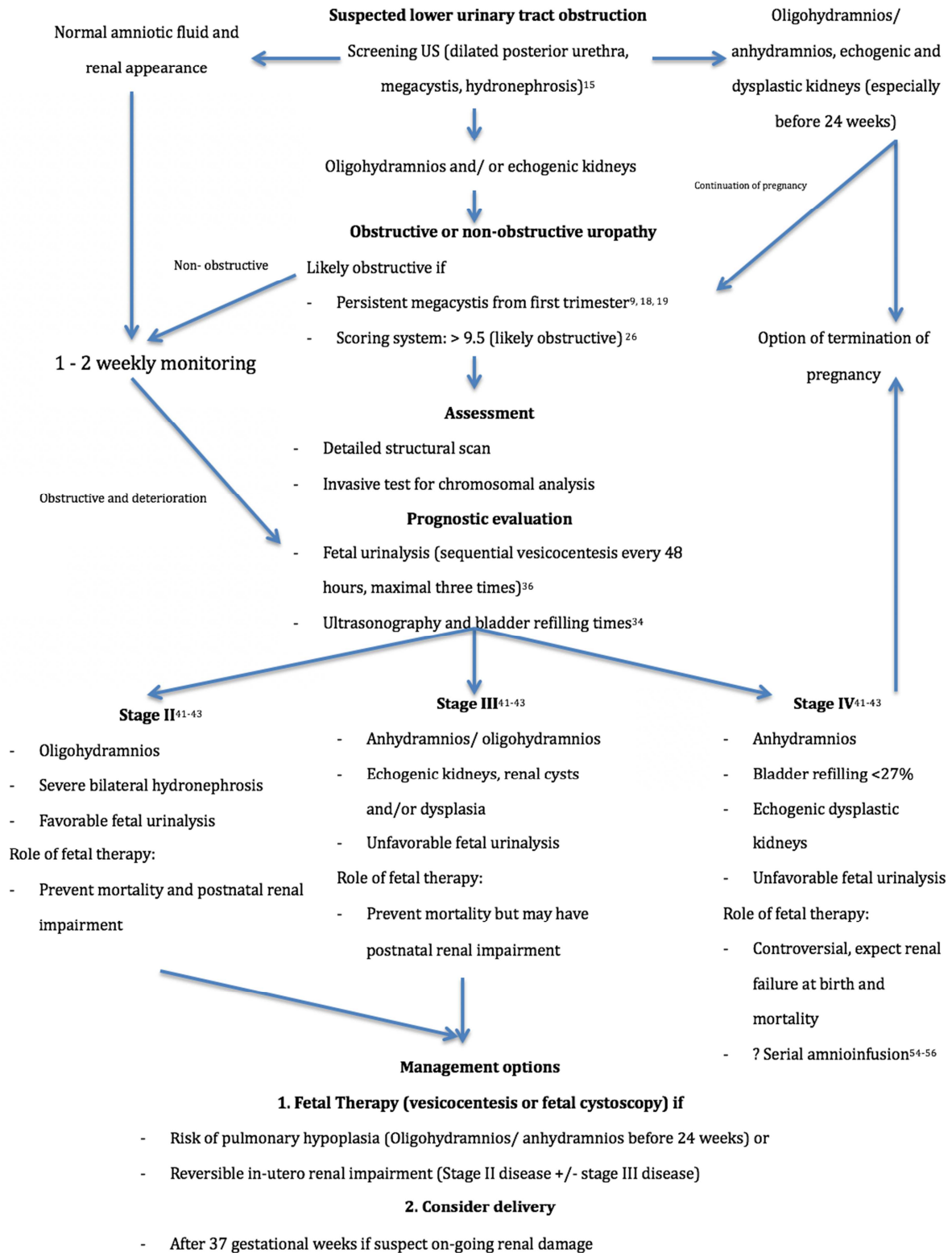
	AUC	95% CI	P value
Classic triad	0.63	0.49-0.77	0.07
Clinical scoring	0.84	0.75-0.93	<0.001



ACCEPTED MANUSCRIPT



ACCEPTED MANUSCRIPT



**Highlight**

- Congenital non-obstructive uropathy can share similar prenatal ultrasonographic characteristic with obstructive uropathy.
- Prognostic estimation is essential before considering fetal therapy
- Fetal intervention may possibly improve perinatal survival but survivors still have a high rate of renal impairment.