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Review article

Current applications of *in utero* intervention for lower urinary tract obstruction

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Summary

Purpose
Since the early 1980s with the inception of fetal intervention for obstructive uropathy, there have been creative attempts to improve both perinatal and long-term outcomes. Despite advances in technology and an improved understanding of lower urinary tract obstruction (LUTO) in the fetus, the results for these therapeutic interventions remain guarded and the long-term renal morbidity among survivors remains problematic.

Recent findings
Fetal LUTO represents a range of disorders but the most common of these is posterior urethral valves (PUVs). Selection criteria for candidates of possible intervention have improved with our understanding of fetal renal physiology. Serial urinalysis has marginally improved our ability to predict those that may ultimately respond to treatment [1,2], but the potential in the development of biomarkers for renal development or maldevelopment holds greater promise [3]. Advancements in fetal surgery may result in less fetal and maternal morbidity, but limited long-term improvement in outcomes highlights the controversial nature of the various interventions [4–10]. We must counsel families that fetal surgery offers hope but we cannot allow them to hold unrealistic expectations for cure.

Summary
In appropriately selected fetuses, intervention may improve perinatal survival but not without risk to mother and fetus. Long-term renal outcomes remain problematic amongst survivors. In the case of PUV, postnatal primary valve ablation remains the cornerstone of treatment for nephron preservation; however, our ability to mimic these results in the prenatal population remains poor [11]. Disease severity has likely predetermined those that will survive through the perinatal period with or without intervention. Nonetheless, our drive to assess and manage fetal obstructive uropathy perseveres so that we may ultimately relieve obstruction and preserve renal and lung function. We must maintain optimism that continued advances will ultimately improve outcomes, but also be realistic with our current expectations. This paper reviews the status of current *in utero* interventions and outcomes.

Introduction

Lower urinary tract obstruction (LUTO) is a devastating cause of renal failure in newborns. It affects 2.2 per 10,000 live births and represents the most common identifiable cause of renal failure in infants and children [11]. While it is possible to relieve the obstruction during the postpartum period in the newborn, research efforts have long aimed at resolving the pathology *in utero* before it causes irreparable renal damage. The experimental basis of these *in utero* interventions has been in animal models [12,13]. Attempts to mimic laboratory successes, although creative, have not been as successful as hoped for. Imaging technology continues to advance, diagnostic criteria for intervention have been delineated, and techniques for intervention have been refined in an attempt to improve patient selection and subsequent immediate and long-term outcomes. However, our overall understanding of congenital obstructive uropathy remains poor, and predicting improved fetal benefit versus increased risk associated with prenatal intervention remains problematic. In appropriately selected fetuses, intervention may enhance perinatal survival, but intervention might not alter long-term prognosis [6,9,11]. Future efforts must be directed to

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specialized centers with significant experience if we hope to improve our ability to manage the fetus *in utero* with maximum benefit and minimal morbidity and mortality for both fetus and mother.

Lower urinary tract obstruction

Fetal LUTO results in a spectrum of disease ranging from decreased amniotic fluid levels to anhydramnios, a mildly dilated bladder to massive megacystis, pelvicaliectasis to renal dysplasia, an asymptomatic neonate to one with severe pulmonary failure, and combinations of all of the above. In cases of LUTO associated with early onset oligohydramnios, perinatal mortality is greater than 50%, and surviving infants often have chronic kidney disease (CKD) [14,15]. LUTO is most commonly associated with posterior urethral valve (PUV), but a variety of disease entities, including urethral atresia, anterior urethral valves, epispadias, cloacal anomalies, bladder atony, megacystis microcolon syndrome, chromosomal aneuploidies, and prune belly syndrome, may present with a similar picture. Distal obstruction, when left unchecked, may ultimately interfere with the branching of collecting ducts and tubular and glomerular formation, although the timing and severity of the insult is poorly understood. A variety of animal models has failed to reproduce the histological changes of renal dysplasia seen in humans, so it is difficult to extrapolate from these studies the absolute effects of congenital obstructive uropathy on the human fetus [1,3,12,16–18]. Accordingly, it is possible that obstruction may not be the sole cause of the renal dysplasia seen in LUTO [16].

Prenatal diagnosis

Ultrasound and magnetic resonance imaging

Ultrasound and magnetic resonance imaging (MRI) remain our best means of evaluating the fetus *in utero* for obstruction. However, despite continued advancements in the technology, neither modality can consistently elucidate the underlying etiology. On antenatal ultrasound, oligohydramnios and the presence of renal cortical cysts are statistically significant predictors of postnatal renal function. Specifically, oligohydramnios has a specificity ranging from 67% to 75% and renal cortical cysts a specificity of 89% for predicting poor renal function (serum creatinine $>$ 1.2 mg/dL) at 1 year of age. However, renal cortical cysts are not a sensitive measure (29%). Increased renal parenchymal echogenicity and cysts in combination were predictive of renal dysplasia at biopsy or autopsy [2]. A UK population-based epidemiological study in 2012 demonstrated a low (46.9%) antenatal detection rate of isolated LUTO, thus reducing the population that could be referred for *in utero* intervention [19].

While not specifically looking at LUTO in the fetus, several studies have pointed towards the utility of using MRI to aid in determining the etiology of urinary tract anomalies in the fetus. These were most often in concert with sonography [20,21]. One study involving fetal MRI confirmed sonographic findings in 61% of cases and directly impacted fetal management in 3% of cases [22]. Like many aspects of LUTO management, this is a field in flux.

Fetoscopy

Three papers, Welsh et al. [23] and Ruano et al. [7,24], evaluated the utility of fetoscopy for intra-uterine LUTO determination; none of the studies were randomized control trials. These studies did show increased sensitivity for diagnosing PUV by direct visualization of the valves versus other causes of "obstruction" (e.g., urethral atresia, prune belly syndrome) with fetoscopy (83.3–100%) over ultrasound (62.5–63.6%) [8]. While these were small series, fetoscopy changed the diagnosis from 25.0% to 36.4% in cases evaluated [23]. Again, this is a developing area of study. It must also be noted that fetoscopy comes with inherent risk to both mother and fetus. In Ruano et al.'s [24] latest series, complications were experienced in 14.7% of cases. These included urologic fistulae and recurrence of LUTO requiring second intervention.

Biomarkers

There has been considerable discussion and research into potential biomarkers of renal maldevelopment. Aspiration and analysis of fetal urine initially demonstrated some promise in evaluation of fetal renal function, helping predict which fetus may benefit from *in utero* intervention (Table 1) [24]. However, in 2007 Morris et al. [26] performed a systematic review of the literature to evaluate the utility of fetal urine analyses in predicting postnatal renal function in congenital LUTO. Many of the studies suggested that elevated fetal urine concentrations of sodium, calcium and β2-microglobulin were found to have trends toward increased likelihood of poor postnatal renal function but there was no significance. Subgroup analyses of these studies also suggested that gestational age plays an important role in interpreting data from urinalyses and subsequent renal function [26].

Ultimately, the fetal urine analytes investigated in these studies could not accurately predict postnatal renal function [25,27,28]. However, a recent study by Klein et al. [30] successfully used fetal urinary peptides to predict postnatal outcomes in bladder outlet obstruction (BOO). This study identified 12 urinary proteins (PUV12) that predicted likelihood for poor renal function postnatally in fetuses with PUV with higher specificity and sensitivity than traditional fetal urine analysis and ultrasound. While the likelihood that we can significantly alter renal prognosis in a reliable

Table 1 Normal fetal urinary biochemistry at 16 weeks' gestation [26].

Marker	Good prognostic factors
Sodium (mg/dL)	<100 mg/dL
Chloride (mg/dL)	<90 mg/dL
Osmolartiy (mg/dL)	<200 mg/dL
β2-Microglobulin (mg/L)	<4.0 mg/L