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Antenatal intervention for congenital fetal lower urinary tract obstruction (LUTO): a systematic review and meta-analysis

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Key message

Antenatal bladder drainage appears to improve perinatal survival in cases of congenital LUTO.

Short titles

Antenatal intervention for congenital LUTO.

ABSTRACT

Objective: To evaluate the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction (LUTO) in improving perinatal survival and postnatal renal function.

Methods: Electronic databases were searched from their inception until May 2018. Selection criteria included randomized controlled trials and controlled non-randomized observational studies including fetuses with ultrasound evidence of LUTO evaluating antenatal intervention for improving perinatal outcomes. Any type of intervention was analyzed. The primary outcome was perinatal survival. The secondary outcome was postnatal survival with normal renal function. The summary measures were reported as summary odds ratio (OR) with 95% of confidence interval (CI).

Results: 10 articles with a total of 355 fetuses were included in the meta-analysis. Inclusion criteria of the selected studies were singleton pregnancy with severe LUTO confirmed on detailed fetal ultrasound examination. Nine studies,analyzed the efficacy of vescico-amniotic shunt performed in the second trimester. The overall estimate survival was higher in the vesico-amniotic shunt group compared to the conservative group (OR 2.54, 95% CI 1.14 to 5.67). 64/112 fetuses (57.1%) survived in the vescico-amniotic shunt group compared to 52/134 (38.8%) in the control group. Five studies

reported on postnatal renal function between 6 months and 2 years. Postnatal renal function was higher in the vescico-amniotic shunt group compared to the conservative group (OR 2.09, 95% CI 0.74 to 5.9). Fetal cystoscopy was performed in only two included studies.Overall, 45 fetuses underwent fetal cystoscopy. The perinatal survival was higher in the cystoscopy group compared to the conservative management group (OR 2.63, 95% CI 1.07 to 6.47). Normal renal function was noted in 13/34 fetuses in the cystoscopy group versus 12/61 in the conservative management group at 6 month follow-up (OR 1.75, 95% CI 1.05 to 2.92)

Conclusions: Antenatal bladder drainage appears to improve perinatal survival in cases of LUTO. Further randomized trials with long-term follow-up are required to determine the role of antenatal treatment in clinical setting.

INTRODUCTION

Congenital lower urinary tract (bladder neck) obstruction (LUTO) comprises a heterogeneous group of conditions, including congenital posterior urethral valves (PUV) and urethral atresia.[1] They are the

leading cause of pediatric end-stage kidney disease,[2] and have been associated with a mortality rate as high as 45%.[1]

The accuracy of antenatal ultrasound for detection of the condition has been improved in the last years.[3] LUTO in a male fetus presenting with megacystis in the first or second trimester of pregnancy is as likely to reflect urethral atresia or stenosis as it is PUV.[3]

Although postnatal correction of LUTO relieves the urinary obstruction, it is usually too late to rescue the renal and respiratory consequences.[4-6] Several antenatal techniques have been studied in attempts to improve the outcomes of the condition. The most common antenatal treatment are serial ultrasound-directed vesicocentesis, vescico-amniotic shunting, fetal cystoscopy and valve ablation.[1] Some authors have also been reported cases describing open surgical correction.[1]

The aim of this systematic review was to evaluate the effectiveness of antenatal intervention for the treatment of LUTO in improving perinatal survival and postnatal renal function.

METHODS

Search strategy

This review was performed according to a protocol designed a priori and recommended for systematic review.[7]Electronic databases (i.e. MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect, the Cochrane Library at the CENTRAL Register of Controlled Trials, Scielo) were searched from their inception until May 2018. Search terms used were the following text words: urethral obstruction, prune belly syndrome, enlarged bladder, congenital urinary tract obstruction, LUTO, posterior valves, fetal therapies, fetal cystoscopy, and vescico-amniotic shunt. No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (GS, ER). Differences were discussed and consensus reached.

Selection criteria

Selection criteria included randomized controlled trials and controlled non-randomized observational studies including fetuses with ultrasound evidence of LUTO (i.e. enlarged bladder, bilateral hydronephrosis, keyhole sign) evaluating antenatal intervention for improving perinatal outcomes. Any type of intervention was analyzed, including bladder drainage via vesicocentesis, vesico-amniotic shunt, and fetoscopic surgery, such as fetal cystoscopy, and ablation of valves. Open fetal bladder

surgery was also included. Uncontrolled observational studies, case reports, and case series were excluded.

Data extraction and risk of bias assessment

Two reviewers (GS, ER) independently judged the methodological quality of studies included in the meta-analysis. For non-randomized studies we used a modified version of the "Newcastle-Ottawa Scale".[8] Quality of studies was evaluated in four different domains: "selection", "comparability", "exposure", and "outcome". Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias.

For randomized trials, the risk of bias was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[7] Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias.[7]

Any discrepancies concerning author's judgements were referred to a third reviewer (AV) and resolved by consensus.

Outcomes

Primary and secondary outcomes were defined before data extraction. The primary outcome was perinatal survival. The secondary outcome was postnatal survival with normal renal function. Outcomes were assessed separately by the type of intervention,

Statistical analysis

The data analysis was completed independently by two authors (GS, AV) using Review Manager v. 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by discussion.

The summary measures were reported as summary odds ratio (OR) with 95% of confidence interval (CI). The random effects model of DerSimonian and Laird was used due to anticipated heterogeneity among selected studies. I-squared (Higgins I^2) greater than 0% was used to identify heterogeneity. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. A 2 by 2 table was assessed for OR. Data were extracted and imported into Review Manager. Potential publication biases were assessed statistically by using Begg's and Egger's tests. P value <0.05 was considered statistically significant.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[9]

RESULTS

Study selection and study characteristics

Selection flow chart is shown in Figure 1. A total of 10 articles with a total of 355 fetuses were included in the meta-analysis.[10-19] Publication bias, assessed using Begg's and Egger's tests, was not significant (P=0.84 and 0.80 respectively), suggesting that all relevant articles have been included. Statistically heterogeneity within the trials was low with no inconsistency for the primary outcome.

The characteristics of the included studies are summarized in Table 1. Nine studies were controlled observational studies. Only one study had randomized study design. The interventions were undertaken between 16 and 28 weeks, in the studies that reported. The overall risk of bias was judged as low, with most of the included studies having low risk of bias (Figure 2, Figure 3). Regarding the interventions, the majority were vescico-amniotic shunts.

Inclusion criteria of the selected studies were singleton pregnancy with severe LUTO confirmed on detailed fetal ultrasound examination, including an extremely dilated bladder with increased wall thickness ('megabladder') associated with a dilated urethra ('keyhole sign'). Severe LUTO included PUV in the vast majority of the cases, vesicoureteral reflux, urethral atresia, urethral stenosis, Prune Belly syndrome, cloacal dysgenesis, cloacal anomaly, megacystis-microcolon syndrome, and megalourethra. Studies included only pregnancies with no additional fetal malformations. Criteria for a good predicted prognosis were: Na <100 mEq/l, Cl <90 mEq/l, osmolarity <210 mOsm/l, beta-2-microglobulin <2 mg/dl.

Synthesis of results

Vescico-amniotic shunt

Nine studies,[10-18] conducted between 1990 and 2015, analyzed the efficacy of vescico-amniotic shunt performed in the second trimester for LUTO. Of the nine included studies, four were retrospective cohort studies, one was prospective cohort study, one contained combined prospective and retrospective cohorts, one was a randomized trial, and the other two did not specify the method of data collection.

Perinatal survival was reported in all the nine selected studies. The overall estimate survival was higher in the vescico-amniotic shunt group compared to the conservative group (OR 2.54, 95% CI 1.14 to 5.67; Figure 4). We reported 64/112 (57.1%) survived fetuses in the vescico-amniotic shunt group compared to 52/134 (38.8%) in the control group.

In subgroup analysis, the vescico-amniotic shunt was associated with higher perinatal survival among fetuses with non-favorable fetal urinary chemistry, but not among those with favorable fetal urinary chemistry (Figure 4).

Five studies reported on postnatal renal function between 6 months and 2 years. Good postnatal renal function was higher in the vescico-amniotic shunt group compared to the conservative group (OR 2.09, 95% CI 0.74 to 5.9; Figure 5).

Vescicocentesis

Six studies reported outcomes of fetuses after vescicocentesis.[12-17] However none of them reported outcomes comparing vescicocentesis with conservative management, thus this intervention could not be completed in this meta-analysis.

Fetal cystoscopy

Fetal cystoscopy was performed in only two included studies.[11,19] Overall, 45 fetuses underwent fetal cystoscopy. Eleven cases came from Quintero et al. while 34 cases came from Ruano et al. Of the 11 cases reported by Quintero et al. who underwent cystoscopy, 4 received no treatment, 2 received urethral stent placement, 4 standard vescico-amniotic shunt, and one permeation of PUV. Out of them 34 cases of Ruano et al. 12 of them were noticed PUV at the time of cystoscopy.

The perinatal survival was higher in the cystoscopy group compared to the conservative management group (OR 2.63, 95% CI 1.07 to 6.47; Figure 6). Long-term follow-up was reported only by Ruano et al. Normal renal function was noticed in 13/34 fetuses in the cystoscopy group versus 12/61 in the conservative management group at 6 month follow-up (OR 1.75, 95% CI 1.05 to 2.92)

Open procedure

One study,[12] included nine fetuses underwent an open procedure by maternal laparotomy and hysterotomy, such as open shunt insertion, bladder marsupialization, or cutaneous uterostomy. No comparison group was provided.

DISCUSSION

Principal findings

This meta-analysis including 10 studies showed that prenatal intervention for congenital LUTO improves perinatal survival. The vast majority used intervention was vescico-amniotic shunt with showed to be associated with also long-term beneficial effects, including higher rate of survival with normal renal function. Data from fetal cystoscopy seems promising but warrants further investigation as the sample size was small.

This review represents the most comprehensive evidence available on efficacy of antenatal treatment for LUTO. An extensive literature search was performed in multiple databases, and the robustness of the methodology is the major strength of the review. This review updated prior review on the topic.[1] Morris et al. performed a meta-analysis of all antenatal interventions for congenital LUTO. However,

they included also uncontrolled studies, and case series, and used different methodology. This review includes more recent evidence, as well as the only RCT addressing this topic.

Interpretation

Prenatal detection of fetal complications may improve outcomes by optimizing antenatal interventions and through a better use and better timing of interventions.[20-26] Ultrasound technology has high sensitivity for urologic anomalies, which account for 20% of all prenatally identified congenital anomalies.[27] Congenital LUTO is a group of conditions primarily affecting the male fetus. The most common cause of LUTO is PUV.[27]

Vesico-amniotic shunting is a treatment option for relief of the urinary obstruction associated with severe LUTO but this procedure is associated with complications such as migration, obstruction and displacement of the shunt tubing.[28] An alternative option to vescico-amniotic shunt, is fetal cystoscopy.[29,30] It has the advantage to help determine the etiology of the urophaty, e.g. PUV, Prune Belly syndrome or urethral atresia. Another potential clinical advantage of fetal cystoscopy as compared to in-utero vesicoamniotic shunting is avoidance of amnioinfusion, which is often needed for shunting. Cystoscopy may also allow the placement of a transurethral catheter in case of urethral stenosis.[29] However, fetal cystoscopy is more complex technically and usually requires special instrumentation and multidisciplinary training at an established center for fetoscopic surgery. It has been also associated with several complications, including fistulas, fetal bleeding and fetal demise.[30] Findings from this review largely came from vescico-amniotic shunting data. Robust evidence for other treatments, including fetal cystoscopy, are lacking and therefore clinical utility of these techniques are still subject of debate due to the small sample size.

Conclusions

In summary, antenatal bladder drainage appears to improve perinatal survival in cases of LUTO. Randomized trials with long-term follow-up are required to determine the role of antenatal treatment in clinical setting.

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TABLES

Table 1. Characteristics of the included studies

	Study location	Type of the study	Sample size*	Type of intervention	GA at intervention**
Crombleholme 1990[12]	USA	Retrospective cohort	40	VC, VAS	Not reported
Nicolini 1991[13]	UK	Not reported	13	VC, VAS	17 - 28
Lipitz 1993[14]	UK	Not reported	19	VC, VAS	19 – 25
Johnson 1994[15]	USA	Retrospective and prospective cohort	22	VC, VAS	14 – 24
Quintero 1995[19]	USA	Retrospective and prospective cohort	13	Cystoscopy	16-24
Freedman 1996[16]	USA	Retrospective cohort	52	VC, VAS	Not reported
McLorie 2001[17]	Canada	Retrospective cohort	9	VC, VAS	20 – 28
Morris 2013[10]	UK, Ireland, and Netherlands	RCT	31	VAS	Not reported
Morris 2015[18]	UK, Ireland, and Netherlands	Prospective cohort	45	VAS	Not reported
Ruano 2015[11]	Brazil and France	Retrospective cohort	111	VAS, cystoscopy	20.2

**Elective termination of pregnancy was excluded.*
***Mean or range in weeks*
VAS, vescico-amniotic shunt; RCT, randomized controlled trial; VC, vescicocentesis;

FIGURES

Figure 1. Flow diagram of studies identified in the systematic review. *(Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).*

Figure 2. Assessment of risk of bias for randomized trials. Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias.

Figure 3. Modified Newcastle-Ottawa risk of bias scoring judgements for non-randomized studies. Summary of risk of bias for each study; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias.

Figure 4. Forest plot for perinatal survival in fetuses with or without vescico-amniotic shunt

Figure 5. Forest plot for good postnatal renal function in fetuses with or without vescico-amniotic shunt

Figure 6. Forest plot for perinatal survival in fetuses with or without fetal cystoscopy

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