The effectiveness of fetal cystoscopy as a diagnostic and therapeutic intervention for lower urinary tract obstruction: a systematic review

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ABSTRACT

Objective To determine the effectiveness of fetal cystoscopy in the prenatal diagnosis of and intervention for congenital lower urinary tract obstruction.

Methods This study was a literature search using Medline, Embase, Cochrane Library, MEDION, Web of Science reference lists and contact with experts. All studies reporting on fetal cystoscopy in lower urinary tract obstruction with data for a 2 × 2 table were selected for review. No language restrictions were applied. There was independent selection of studies, data extraction and quality assessment by two reviewers. Peto odds ratios were calculated as a summary measure of effect.

Main Results A total of 2071 citations were identified and 66 papers selected for detailed evaluation, from which four papers with a total of 63 patients were selected for inclusion. Two papers had results for the use of cystoscopy in diagnosis, showing that fetal cystoscopy altered the ultrasound diagnosis of the underlying pathology in 36.4 and 25.0% of fetuses, respectively. Compared to no treatment, fetal cystoscopic intervention demonstrated an odds ratio for improved perinatal survival of 20.51 (95% confidence interval (CI), 3.87–106.89). However, comparing vesicoamniotic shunt (VAS) with fetal cystoscopy there appeared to be no significant improvement in the perinatal survival odds ratio of 1.49 (95% CI, 0.13–16.97). These results had wide CIs and for cystoscopy vs. VAS, all results crossed the line of no effect.

Conclusion There is little published evidence for the effectiveness of therapeutic fetal cystoscopy as an intervention for congenital lower urinary tract obstruction and the quality of this evidence is poor. It should thus be considered to be an ‘experimental intervention’ and subjected to further investigation. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Fetal lower urinary tract obstruction (LUTO) is a condition associated with high perinatal mortality, dependent upon the association with pulmonary hypoplasia. In addition, such pathology carries a long-term risk for chronic renal impairment in up to 50% of surviving cases1–3. For these reasons fetal intervention has been proposed, with percutaneous vesicoamniotic shunting (VAS) the classic treatment for selected cases4–5. However, this in-utero procedure itself carries potential maternal and fetal risks and has not been validated in randomized trials. At least part of the reported poor outcome is related to poor patient selection for such therapy, with heterogeneity of the underlying pathologies being associated with varying outcomes3–6. In addition, experimental studies suggest that VAS shunts may fail to preserve bladder function, as ‘cyclical voiding’ is required for optimal bladder development5–6. Recently, percutaneous fetal cystoscopy has been proposed for accurate diagnosis and potential differential diagnosis between posterior urethral valves (PVUs) and urethral atresia (UA), both of which may have a similar ultrasound appearance. This would, at least theoretically, allow more appropriate treatment to be targeted to the PVUs, allowing a more physiological release of the pathological urinary tract obstruction5–21.
The objective of this study was to undertake a systematic review of the literature in order to determine the effectiveness of fetal cystoscopy as a tool for prenatal diagnosis of, and therapeutic intervention for, congenital urinary tract obstruction.

**METHODS**

A systematic search was performed in Medline, Embase, Cochrane Library, MEDION, Web of Science, reference lists and contact with experts from inception until September 2010 (Appendix S1). In addition, reference lists of specialist publications were hand searched. All studies reporting on fetal cystoscopy in LUTO with data on diagnostic accuracy or effectiveness were selected. There were no language restrictions.

**Study selection and data extraction procedures**

The initial stage of study selection consisted of scrutinizing the database of retrieved citations by two reviewers (R.K.M. and R.R.) to identify articles from the title and/or abstract. In the final stage of study selection the full papers of identified articles were obtained with final inclusion or exclusion decisions made after independent and duplicate examination of the papers. We included studies that reported fetuses with LUTO that had undergone fetal cystoscopy as either a diagnostic procedure or as an intervention compared to either 'expectant prenatal management' (only vesicocentesis) or VAS.

**Study quality assessment**

All included studies were assessed for quality by the use of the full STROBE statement. The randomized controlled trial was considered to be the ideal study design; efforts to minimize bias, adequate reporting of characteristics of the study population – including potential confounders – and adequate definition of all variables were considered to be important elements for overall study quality. If there was uncertainty, then M.D.K. decided on inclusion of the study or not.

**Data synthesis and analysis of diagnosis**

Ideally in a diagnostic review, data to populate a 2 × 2 table would be extracted, allowing calculation of sensitivity, specificity and likelihood ratios. In this case 2 × 2 data would be calculated from the cases where LUTO was suspected at ultrasound scan, cystoscopy was performed and then the results of the two investigations were compared with a ‘gold standard’ postnatally, i.e. postnatal radiological investigation or postmortem. Where this is not possible data must be reported in a qualitative manner expressing how much added information is provided by a test, in this case fetal cystoscopy.

**Data synthesis and analysis of effectiveness**

Again the ideal would be to obtain data from the included papers from fetal cystoscopy compared with another intervention, e.g. VAS or no intervention, with outcome data to assess effectiveness for perinatal survival and perinatal survival with normal postnatal renal function. This would allow 2 × 2 tables of effectiveness to be calculated for these outcomes. From the 2 × 2 tables the Peto odds ratio with 95% confidence intervals (CI) can be calculated. The Peto odds ratio is based on the observed number of events and number of events expected if there were no differences between the experimental and control groups. It is particularly useful where the numbers are small, and the event rate low, as is the case in this review.

An Excel spreadsheet (Microsoft Corp., Redmont, WA, USA) was used to summarize all results. The effect of fetal cystoscopy compared to no treatment or to VAS was computed for each outcome; overall survival, survival excluding termination of pregnancy (TOP), perinatal survival excluding TOP and survival with normal postnatal renal function. Forest plots were constructed for each group. Subgroup analysis was performed comparing these outcomes for fetuses with confirmed PUV postnatally wherever possible. We inspected for heterogeneity visually and statistically, calculating the Cochrane Q score and the inconsistency square (I²). If greater than 50% was felt to demonstrate significance between study heterogeneity.

Funnel plots, to examine for the presence of publication bias, could not be constructed owing to the small number of studies and sample sizes. All statistical analyses were performed using StatsDirect version 2.7.2. (StatsDirect, Cheshire, UK).

**RESULTS**

Figure 1 summarizes the process of literature identification and selection. From 2071 potentially relevant citations, 66 were retrieved and evaluated in detail. Of these only four papers – including a total of 63 patients – were of suitable topic matter and relevance to allow inclusion. Table 1 details the four studies included in the review and indicates the characteristics of the studies and literature citations that were included in the present analysis. This table also details the outcome measures and definitions used, while Table 2 details the main results of these studies.

The quality assessment of the included studies is shown in Figure 2. There were no eligible randomized controlled trials. The included cohort studies contained relatively small numbers of subjects and only one was of prospective design. Over 75% of studies complied with the STROBE statement elements describing study design, participant eligibility criteria, patient characteristics and follow-up and number of outcome events. However, few studies made efforts to address bias and most were poor in their...
Results of diagnosis

There were only two papers with diagnostic information at cystoscopy with a postnatal confirmation – those by Ruano et al.20 and Welsh et al.21. In the paper by Ruano et al., there were 11 cases of suspected PUV at ultrasound scan20. Cystoscopy changed the diagnosis in four (36.4%) cases to UA. All the diagnoses at fetal cystoscopy were confirmed postnatally. Thus, the sensitivity of ultrasound for diagnosing PUV was 63.6% with 7 true positives (TP) and 4 false positives (FP). The sensitivity at cystoscopy for both PUV and UA was 100%.

In the paper by Welsh et al. there were eight cases of suspected PUV on ultrasound scan with a cystoscopic and postnatal diagnosis21. Cystoscopy changed the diagnosis in two (25.0%) cases (one to UA and one to prune belly syndrome (PBS)). There was a single case of suspected PUV at ultrasound scan and cystoscopy that was postnatally diagnosed as UA. In this study, the sensitivity of ultrasound for PUV was 62.5% (5 TP and 3 FP) and for cystoscopy it was 83.3% (5 TP and 1 FP). The sensitivity of cystoscopy for PBS and UA was 100%.

Results of effectiveness

The results for effectiveness are described for the individual studies and displayed in Figures 3 and 4. In the study by Holmes et al.9 results were available for 11 fetuses that underwent antenatal intervention with postnatal outcomes. All were suspected cases of PUV at ultrasound scan. Two fetuses had laser ablation of valves with one of these fetuses also having a VAS inserted. This fetus was thus excluded from the analysis. Nine fetuses were managed with VAS. Thus data were available to calculate an odds ratio for cystoscopic treatment vs. VAS for 10 fetuses (Figure 3).

In the study by Quintero et al.17 11 fetuses had cystoscopy performed for suspected LUTO. The antenatal interventions performed were insertion of two urethral stents, one ‘permeation of valves’ with probing and nine percutaneous VAS insertions; four fetuses had no intervention. Comparisons could only be made between cystoscopy and VAS and cystoscopy and no treatment. There were no outcome data for one of the fetuses with expectant management, leaving 10 fetuses for analysis (Figures 3 and 4).

In the study by Ruano et al.20, 11 fetuses underwent fetal cystoscopy while seven that were diagnosed at cystoscopy with PUV had laser ablation. Twelve fetuses had expectant management (no intervention). All fetuses had suspected PUV at ultrasound scan. Thus comparisons could be made between laser fulguration of valves and expectant management (Figure 4).

In the study by Welsh et al.21 there were thirteen fetuses with suspected PUV on ultrasound scan that underwent cystoscopy, with 10 having a prenatal intervention. The interventions included one hydroablation only; two hydroablation and guidewire passage; four guidewire passage only; one hydroablation, guidewire and percutaneous VAS; and two guidewire passage and percutaneous VAS. Three fetuses had no intervention following cystoscopy and there were no outcome data available for these fetuses. The three fetuses that had cystoscopic intervention and VAS were also excluded from the analysis. There were thus seven fetuses with outcome data but all were treated as VAS; and two guidewire passage and percutaneous VAS. Only two of these fetuses had a VAS inserted. This fetus was thus excluded from the analysis.
Table 1 Characteristics of included studies in systematic review of effectiveness of fetal cystoscopy for congenital lower urinary tract obstruction

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Data collection</th>
<th>Population</th>
<th>Primary diagnosis</th>
<th>Additional prognosis</th>
<th>Intervention</th>
<th>Outcome of intervention</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al.</td>
<td>Cohort</td>
<td>Retro</td>
<td>Location: USA; dates: 1981–1999</td>
<td>All patients with a prenatal diagnosis of obstructive uropathy (bilateral hydronephrosis, an enlarged bladder with dilated posterior urethra and oligohydramnios), fetal intervention undertaken, follow-up undertaken for those patients with postnatal diagnosis of PUV</td>
<td>All PUV</td>
<td>All favorable prognosis on urinalysis (Na⁺ &lt; 100 mEq/L, Cl⁻ &lt; 90 mEq/L, osmolality &lt; 210 mOsm/L), 2 patients abnormal renal appearance (cysts/increased parenchymal echogenicity)</td>
<td>1 cutaneous ureterostomy, 2 fetal bladder marsupialization, 2 endoscopic laser ablation of valves, 9 VAS</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Quintero et al.</td>
<td>Cohort</td>
<td>NS</td>
<td>Location: USA; dates: NS</td>
<td>13 fetuses with features of lower obstructive uropathy diagnosed on ultrasound scan at mean 20.5 (range, 16–28) weeks and having a normal karyotype. 7 had decreased amniotic fluid volume, 6 increased renal echogenicity, 10 hydroureter</td>
<td>5 PUV, 1 megacystic-microcolon syndrome, 1 urethral atresia, 3 PBS 1 unknown, 2 NS</td>
<td>Predicted prognosis based on urine biochemistry (7/11 good, 4/11 poor prognosis) (Johnson 1994)</td>
<td>13 VC, 6 VAS (4 standard percutaneous, 2 urethral), 1 permeation of PUV, 11 fetal cystoscopy</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Ruano et al.</td>
<td>Cohort</td>
<td>Pro</td>
<td>Location: Brazil; dates: 2006–2008</td>
<td>Fetal cystoscopy offered to patients with severe LUTO prior to 26 weeks with favorable urinanalysis. INC: singleton, severe LUTO (dilated bladder, increased wall thickness and dilated posterior urethra), bilateral hydronephrosis, no other structural anomalies, anhydramnios, GA &lt; 26 weeks, favorable urinanalysis Na⁺ &lt; 100 mEq/L, Cl⁻ &lt; 90 mEq/L; osmolality &lt; 210 mOsm/L; normal fetal karyotype</td>
<td>14 PUV, 1 PUV + PB, 8 UA</td>
<td>Favorable urinanalysis Na⁺ &lt; 100 mEq/L, Cl⁻ &lt; 90 mEq/L; osmolality &lt; 210 mOsm/L; normal fetal karyotype</td>
<td>11 Fetal cystoscopy, 5 endoscopic laser ablation of valves, 12 expectant</td>
<td>Adequate</td>
</tr>
</tbody>
</table>
Fetal cystoscopy in lower urinary tract obstruction

Adequate 16-34 PUV, 1 urethral atresia, 1 PBS urinalysis (Na > 100 mmol/L, Cl > 80 mmol/L, osmolality > 200 mOsm/L) 4/13 poor prognosis

Good prognosis on amniocentesis (Na > 100 mmol/L, Cl < 80 mmol/L, osmolality < 200 mOsm/L) 13 Fetal cystoscopy, 6 guidewire, 3 hydroablation and guidewire, 1 hydroablation only, 3 VAS, 3 no further intervention

11 PUV, 1 urethral atresia, 1 PBS

Cohort Retro Location: UK; dates: 1997-2002


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Patients with no intervention were those in whom PUV was confirmed postnatally and TOP were excluded.

In the cystoscopy group 3/23 (13.0%) opted for TOP compared with 1/13 (7.7%) and 6/15 (40.0%) in the VAS and no intervention groups, respectively. There were two miscarriages in the cystoscopy group following preterm premature rupture of membranes. Other complications following cystoscopy included urinary ascites and a case of bladder perforation (Table 2).

DISCUSSION

Because congenital LUTO is associated with increased perinatal and infant mortality and morbidity, a series of antenatal interventions have been proposed in an attempt to prevent postnatal complications. The optimal management of fetuses with LUTO continues to be one of the most challenging subjects in the field of fetal intervention and therapy. The rationale for a prenatal intervention is based on the prevention of neonatal death due to severe pulmonary hypoplasia and an overall improvement in long-term renal outcome. Ultrasound-guided percutaneous placement of a VAS has been the most widely performed antenatal intervention, initially reported by Golbus et al. in 1982. Since that time the efficacy of prenatal treatment in improving renal function and delaying progression to chronic end-stage renal disease has yet to be definitively demonstrated.

A recent systematic review indicates potentially improved survival of babies with LUTO treated in this way, but there are concerns that long-term childhood morbidity is not improved and may be worsened.

Percutaneous fetal cystoscopy has been reported as an alternative therapeutic option for the in-utero treatment of LUTO. It has theoretical advantages over VAS, as it allows anatomical diagnosis and ablation of the PUV (if visualized) by direct instrumentation of the proximal urethra. However, if UA is identified, ablation cystoscopically, thus there were no comparisons that could be made. The outcomes for these fetuses were one TOP, one miscarriage, one intrauterine death at 36 weeks, one neonatal death and three survivors, of which two had impaired renal function.

It was not possible to compare cystoscopy with vesicocentesis as there were no data for the outcome in the vesicocentesis group in one paper and in the other, where vesicocentesis was reported, this was not considered to be therapeutic by the study authors, as only the fetal renal pelvis was aspirated for urinary analysis.

Compared to no treatment, fetal cystoscopic intervention showed an odds ratio for improved perinatal survival of 20.51 (95% CI, 3.87–108.69). But on comparing VAS with fetal cystoscopy there appeared to be no significant improvement in perinatal survival (odds ratio, 1.49 (95% CI, 0.13–16.97)). These results, however, had wide CIs, and for cystoscopy vs. VAS, all results crossed the line of no effect. There was no statistically significant heterogeneity.

Subgroup analysis was performed looking at those cases where PUV was confirmed postnatally and TOP were excluded.

In the cystoscopy group 3/23 (13.0%) opted for TOP compared with 1/13 (7.7%) and 6/15 (40.0%) in the VAS and no intervention groups, respectively. There were two miscarriages in the cystoscopy group following preterm premature rupture of membranes. Other complications following cystoscopy included urinary ascites and a case of bladder perforation (Table 2).
Table 2 Study results for included studies in systematic review of effectiveness of fetal cystoscopy for congenital lower urinary tract obstruction

<table>
<thead>
<tr>
<th>Study</th>
<th>Vesicocentesis</th>
<th>Cystoscopy</th>
<th>Outcome (survival)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al.9</td>
<td>Cases: 14</td>
<td>Cases: 14</td>
<td>Indication: NS</td>
<td>1 multiple shunts due to malfunction or migration, 1 laser ablation of valves</td>
</tr>
<tr>
<td></td>
<td>GA: NS</td>
<td>GA: Mean 22.5 (range, 19–30) weeks</td>
<td>Technique: NS</td>
<td>required VAS due to urinary ascites</td>
</tr>
<tr>
<td></td>
<td>Technique: US-guided percutaneous fetal bladder aspiration</td>
<td>Duration: NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Volume: NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number: Serial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quntero et al.17</td>
<td>Cases: 13</td>
<td>Cases: 6</td>
<td>Indication: NS</td>
<td>2 membrane separation &amp; 1 perforation of post bladder wall cystoscopy</td>
</tr>
<tr>
<td></td>
<td>GA: NS</td>
<td>GA: 16–28 weeks</td>
<td>Technique: fetal cystoscopy, standard VAS or urethral VAS. Amnioinfusion in oligohydramnios Duration: NS</td>
<td>2/13 failed – VAS</td>
</tr>
<tr>
<td></td>
<td>Technique: Johnson (1994)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Volume: NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number: serial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruano et al.20</td>
<td>Cases: 23</td>
<td>Cases: 11</td>
<td>Indication: Fetal cystoscopy offered to patients with severe LUTO prior to 26 weeks with favorable urinalysis, INC: singleton, severe LUTO (dilated bladder, increased wall thickness and dilated posterior urethra), bilateral hydroureter, no other structural anomalies, anhydronephrosis, GA &lt; 26 weeks, normal fetal karyotype GA: mean 20.7 (range, 19–24) weeks Technique: Performed under maternal epidural fetal anesthesia with fentanyl and pancuronium, US guidance of 22-gauge needle into either umbilical vein or fetal arm muscle. 2.2 mm curved operating sheath with 3 separate channels and obturators. Fetoscope with 1.0 mm; PUV laser Nd : YAG. At diagnosis of urethral atresia procedure was ended with no intervention.</td>
<td>All fetuses undergoing cystoscopy had mild ascites following a procedure that resolved spontaneously. No maternal death, blood transfusion, infection. 3/8 cystoscopy had PROM and 2/8 preterm labour. 3/9 expectant had PROM and 3/9 Preterm labour. No abruptions in either group.</td>
</tr>
<tr>
<td></td>
<td>GA: &lt; 26 weeks</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Technique: percutaneous puncture of less dilated renal pelvis 22-G needle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Volume: NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number: NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fetal cystoscopy in lower urinary tract obstruction

2 fetal losses (1 after VAS, 1 after cystoscopy), 5 cases had urinary ascites after cystoscopy. Cystoscopy and aspiration of urine only: no results available for 3 cases. Duration: mean 39.5 (range, 20–60) min. Guidewire only: Alive: 1/4 (Renal impairment); Dead: 2/4 (TOP, IUD). Hydroablation and guidewire: Alive: 1/2 (Renal impairment); Dead: 1/2 (TOP). Hydroablation, guidewire and VAS: Alive: 1/1 (NI). Duration: NS. Cases: 0. Weihl et al.21 proposed fetal cystoscopy as a diagnostic approach for severe fetal LUTO. The diagnosis of UA using ultrasound, confirmed by cystoscopy, is likely to be better the earlier in gestation that the diagnosis is made, with a corresponding worsening in overall prognosis as gestation proceeds36. Despite these observations, ultrasonography has a relatively poor ability to differentiate the causes of obstructive uropathy since the ‘keyhole sign’ on ultrasound examination has high sensitivity but low specificity for the diagnosis of PUV37 and for defining long-term prognosis37,38. In this review the sensitivity of cystoscopy for detecting PUV was between 87.5 and 100%, but previous studies have reported figures for ultrasound as low as 45%36. The use of fetal cystoscopy in the prenatal diagnosis to specifically differentiate between PUV and UA has also been demonstrated recently by Ruano et al.20 This systematic review of the literature evaluates the effectiveness of fetal cystoscopy in allowing the correct prospective diagnosis of LUTO and suggests high sensitivity (100%) and specificity (85.7%). We were unable to perform a diagnostic accuracy systematic review according to recommended methodology23–25 owing to the nature of the evidence available. None of the included papers were diagnostic accuracy studies and thus while the sensitivity of cystoscopy and ultrasound as diagnostic tools can be evaluated there are no data available to calculate specificity.

The effectiveness of fetal cystoscopy for the prenatal therapy of LUTO was evaluated with regard to perinatal survival and postnatal renal impairment. This critical appraisal of the literature indicates that perinatal survival is increased only when comparison is made between fetal cystoscopy and expectant prenatal management. It does not demonstrate improved perinatal mortality or morbidity when compared with VAS. The inferences made from these results have to be interpreted, however, with careful consideration of the limitations of the available evidence and potential for bias. The evidence consists of a small number of studies with small sample sizes and hence wide CIs, there is heterogeneity in treatment protocols, and none of the studies document long-term pediatric follow-up to allow for the evaluation of childhood bladder function and voiding morbidity in these groups.

The present systematic review supports the concept of further randomized controlled trials comparing fetal cystoscopy with VAS. However, such a study would need to recruit a relatively large number of pregnancies (to detect differences in long-term morbidity), avoid selection bias and circumvent recent data indicating a predisposition of parents to choose TOP. As such, there would need to be post-hoc analysis of outcomes depending upon the bladder appearance at cystoscopy and on ultrasound (i.e., grossly enlarged, thin-walled or moderately enlarged, thick-walled bladders). As for the diagnostic component, a systematic review of effectiveness should be performed...
Figure 2 Bar chart showing quality assessment of primary studies included in a systematic review of effectiveness of fetal cystoscopy for congenital lower urinary tract obstruction. □, Yes; ■, no; ■, unclear; ***, not applicable.

Figure 3 Effect of fetal cystoscopy vs. vesicoamniotic shunting (VAS) on perinatal survival. PUV, posterior urethral valve; TOP, termination of pregnancy.

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1 according to recommended methodology; in this study these guidelines were followed as closely as the quality of the evidence allowed.

2 In conclusion, there is very little published evidence for the effectiveness of fetal cystoscopy as a diagnostic and therapeutic intervention for LUTO, and the quality of this evidence is poor. Fetal cystoscopy should thus be considered to be an experimental intervention and further evidence, including a very well designed randomized controlled trial, is required to assess its effect on perinatal

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Fetal cystoscopy in lower urinary tract obstruction

<table>
<thead>
<tr>
<th>Survival All</th>
<th>Favors no intervention</th>
<th>Peto odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintero et al.(^1) n = 6</td>
<td>2/3 0/3</td>
<td>12.18 (0.55 – 270.15)</td>
</tr>
<tr>
<td>Ruano et al.(^2) n = 23</td>
<td>5/7 1/16</td>
<td>25.36 (3.51 – 183.39)</td>
</tr>
<tr>
<td>Pooled result Q = 0.16, P = 0.69</td>
<td></td>
<td>20.51 (3.87 – 108.69)</td>
</tr>
<tr>
<td>Ruano et al. PUV only n = 14</td>
<td>5/7 1/7</td>
<td>8.73 (1.14 – 67.13)</td>
</tr>
<tr>
<td>Survival excluding TOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruano et al. n = 17</td>
<td>5/6 1/11</td>
<td>21.32 (2.83 – 160.62)</td>
</tr>
<tr>
<td>Ruano et al. PUV only n = 11</td>
<td>5/6 1/5</td>
<td>10.20 (1.05 – 98.97)</td>
</tr>
</tbody>
</table>

Figure 4 Effect of fetal cystoscopy vs. no intervention on perinatal survival. PUV, posterior urethral valve; TOP, termination of pregnancy.


REFERENCES


**SUPPORTING INFORMATION ON THE INTERNET**

The following supporting information may be found in the online version of this article:

**Appendix S1:** Search strategy for systematic review of effectiveness of antenatal intervention for congenital lower urinary tract obstruction.
QUERIES TO BE ANSWERED BY AUTHOR & EDITOR

IMPORTANT NOTE: Please list all query corrections in an e-mail and send to the production contact as detailed in the covering e-mail, or mark all corrections directly on the proofs and send the scanned copy via e-mail. Please do not send corrections by annotated PDF file and do NOT mark your corrections on this query sheet.

Queries to Author:

AQ1 Numbers for authors’ affiliations changed to symbols as per style – but in the original MS only numbers 1 to 3 were listed against the authors’ names, while four institutional addresses are given; please check.

AQ2 Please check that all affiliations are correct and complete.

AQ3 The shades of grey in Figure 2 were difficult to distinguish; could you please check the figure very carefully to ensure that it has been interpreted correctly. Also, the bottom 8 bars are labelled but the top 12 are not. Could you provide the appropriate labels?

AQ4 Is this the correct address for Microsoft?

AQ5 Would you mind checking the sense of ‘I² greater than 50% was felt to demonstrate significant between study heterogeneity’? I’ve changed ‘significant’ to ‘significance’; but between significance and what?

AQ6 Would you mind checking this, as Table 2 seems to indicate that there were only 6 fetuses that had cystoscopy in this study?

AQ7 Would you mind checking these data, as Table 1 seems to indicate that there were 6 guidewires, 3 hydroablation and GW, and 1 hydroablation only.

AQ8 I’ve attempted to simplify this table by introducing two extra columns and taking diagnosis and prognosis from the fourth column; is that OK? Also, what does INC mean in the 3rd entry of column 4 (and also in Table 2)? Ca is given in the key, but does not appear in the table, so I’ve deleted it – or should some data appertaining to calcium be added? In ‘Additional prognosis’ osmolarity was used twice and osmolality once, so I’ve changed the latter to the former – is that the right way round? And I figure that as regards osmolarity, then mOsm/L is correct, not Osm/L as in the first occurrence. Finally I’ve added + and − signs to Na and Cl; OK?

AQ9 ‘The diagnosis of urethral atresia using ultrasound, confirmed by cystoscopy, is likely to be greater the earlier gestation that the diagnosis is made with a corresponding worsening in overall prognosis’ changed to: ‘The diagnosis of UA using ultrasound, confirmed by cystoscopy, is likely to be better the earlier in gestation that the diagnosis is made, with a corresponding worsening in overall prognosis as gestation proceeds’; is that the correct interpretation?

AQ10 ‘in this study’ added here; OK?

AQ11 Have refs. 14, 25 & 26 been styled correctly as books?

Queries to Editor:

EQ1 Please check and confirm shading of the figure.
After receipt of your corrections your article will be published initially within the online version of the journal.

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