Ultrasound Obstet Gynecol 2017; **49**: 696–703
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15988

Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis

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KEYWORDS: fetal obstructive uropathy; posterior urethral valve; vesicoamniotic shunt

ABSTRACT

Objective *To evaluate the effect on perinatal and postnatal survival of vesicoamniotic shunt (VAS) as treatment for fetal lower urinary tract obstruction (LUTO).*

Methods *An electronic search of Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus using relevant search terms was conducted from inception to June 2015 to identify studies comparing outcomes of VAS* vs *conservative management for treatment of LUTO. Cohort studies and clinical trials were considered eligible. Single-arm studies and studies that did not report survival were excluded. Sample size and language were not criteria for exclusion. Two reviewers extracted independently data in a standardized form, including study characteristics and results. Primary outcomes were perinatal and postnatal survival. Secondary outcome was postnatal renal function. Data on fetal survival were expressed as odds ratio (OR) and 95% CI.*

Results *Of the 423 abstracts retrieved, nine studies were eligible for inclusion. These studies included 112 fetuses treated with VAS and 134 that were managed conservatively. There was heterogeneity in study design. Although the data demonstrated a difference in effect estimates between the study arms in terms of perinatal survival (OR, 2.54 (95% CI, 1.14–5.67)), there was no difference in 6–12-month survival (OR, 1.77 (95% CI, 0.25–12.71)) or 2-year survival (OR, 1.81 (95% CI, 0.09–38.03)). In addition, there was no difference in effect on postnatal renal function between fetuses that underwent intervention and those that did not (OR, 2.09 (95% CI, 0.74–5.94)).*

Conclusions *Available data seem to support an advantage for perinatal survival in fetuses treated with VAS compared with conservative management. However, 1–2-year survival and outcome of renal function after VAS procedure remain uncertain. Further studies are necessary to evaluate the effectiveness of fetal intervention for LUTO based on different severity of the disease, due to the very low quality of the studies according to GRADE guidelines. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Congenital lower urinary tract obstruction (LUTO) occurs in approximately 2.2 per 10 000 live births[1]. It is more common in males than in females. The most common cause of LUTO is a posterior urethral valve (PUV), which occurs almost exclusively in male fetuses[2]. Other less common causes include mid-urethral hypoplasia, anterior urethral valve, urethral stenosis, ureterocele and urethral agenesis and strictures which can occur in females and present clinically as similar to PUV[2].

LUTO is often associated with severe oligohydramnios, which can lead to pulmonary hypoplasia and, ultimately, neonatal death[3]. Furthermore, 25–30% of those who survive develop end-stage renal disease requiring dialysis and renal transplantation by the age of 5 years[4]. LUTO

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Accepted: 31 May 2016

is usually diagnosed by ultrasound at the time of the routine second-trimester fetal anatomical assessment[5] by the classic features of megacystis with keyhole sign (due to dilated proximal urethra), hydronephrosis and oligohydramnios, with or without cystic renal changes[5]. The most severe forms of LUTO can be diagnosed during the first trimester[6,7].

Although postnatal correction of LUTO relieves the urinary obstruction, it is usually too late to rescue the renal and respiratory consequences of the obstruction[3]. *In-utero* percutaneous vesicoamniotic shunt (VAS) is the most common antenatal treatment in these cases. VAS uses a double pigtail catheter, inserted under ultrasound guidance, to relieve the urinary obstruction by providing bladder drainage and restoring amniotic fluid volume[8]. However, its use is not free from complications, which can occur in up to 40% of cases[9], and the effect on long-term renal function is uncertain[10], despite reported improved survival[10,11].

The objective of this meta-analysis was to investigate the effectiveness of VAS on survival in cases of congenital LUTO, and to update the previously published systematic reviews[10,11] following the publication of the PLUTO trial[5] and other recent studies.

METHODS

Electronic search and information sources

A search was conducted for publications comparing outcomes in fetuses with LUTO that were treated with VAS or by conservative management. A comprehensive search of several databases was conducted in any language from inception of the database to 29 June 2015. The databases were Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary, supplemented with keywords, was used to search for studies on antenatal intervention for the treatment of congenital LUTO, using the terms 'fetal' OR 'congenital' AND 'lower urinary tract obstruction' OR 'posterior urethral valves' OR 'urethral agenesis' AND 'vesicoamniotic shunt' OR 'bladder drainage' OR 'fetal therapy' OR 'fetal intervention'. A secondary search of references of relevant research and review articles was conducted. References from previous systematic reviews/meta-analyses were included in the initial selection. Details of the search strategy are provided in Appendix S1.

Eligibility criteria and study selection

Studies that reported perinatal and postnatal outcomes after VAS, in comparison with conservative management, were selected initially. Principally, cohort studies and clinical trials were included. However, case series were also included if both intervention and conservative management could be identified after exclusion of cases that underwent elective termination of pregnancy (TOP). Single-arm studies and studies that did not report survival were excluded. Neither sample size nor language was a criterion for exclusion. We included studies that clearly defined LUTO by the presence of an enlarged fetal bladder and bilateral hydronephrosis[12,13]. No attempt was made to include or exclude studies according to fetal gender. The primary outcomes of the study were perinatal and postnatal survival rates. The secondary outcome was the effect of VAS on postnatal renal function compared with conservative prenatal management. Screening of retrieved abstracts for selection of eligible studies was achieved independently by two reviewers from different institutions. Discrepancies were minor and were resolved by consensus between reviewers.

Data collection

A standardized form was used to abstract data from selected studies. The form included the author name, study setting, year of publication, type of study, time frame during which the study was conducted, sample size, criteria of fetuses that underwent intervention (gestational age at intervention, presence of fetal anomalies, renal function at time of intervention), gestational age at delivery, renal function and survival. Survival in the perinatal period up to 6 months of age, at 6–12 months and at 2 years of age was reported as odds ratios (ORs). Selected studies were evaluated for risk of bias; the Newcastle–Ottawa Scale (NOS) was used for observational studies and Jadad scoring (Oxford Quality Scoring System) for randomized clinical trials[14–16]. Overall quality of evidence was evaluated using the GRADE scoring system[17].

Statistical analysis

Data were expressed as OR and 95% CI, and were illustrated in forest plots. A random-effects model was applied due to anticipated heterogeneity among selected studies[18]. Significant heterogeneity was considered if I^2 was > 50% or Q-test P-value was < 0.10[19]. For analyses pooling more than 10 studies, a funnel plot was used to assess publication bias. Statistical analysis was performed using Review Manager (RevMan) v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen)[20].

RESULTS

A total of 423 abstracts were retrieved initially and 390 did not meet study inclusion criteria. The remaining abstracts underwent full manuscript review, of which 17 studies were not eligible based on consensus between the reviewers (studies were case reports or case series).

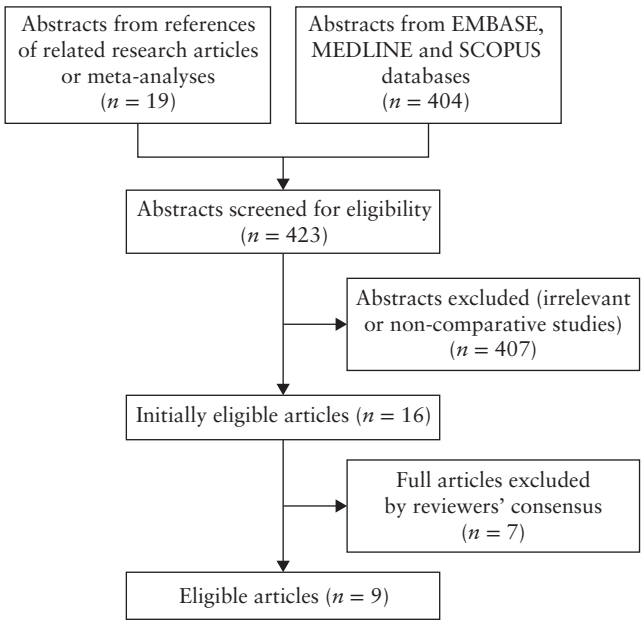

Figure 1 Flowchart summarizing study selection.

Of the remaining 16 studies describing cohorts of fetuses that underwent VAS placement, seven were excluded due to lack of adequate reporting of outcomes or loss of one study arm after exclusion of elective TOP. Nine studies[5,9,21–27] were pooled for meta-analysis (Figure 1).

The nine studies were conducted between 1990 and 2015. Four were retrospective[9,21,25,26] and one was prospective[27] in design, one contained combined prospective and retrospective cohorts[24] and one was a randomized trial[5]. The other two studies did not specify the method of data collection[22,23]. In terms of study setting, three studies were conducted in the USA[21,24,25], two in the UK[22,23], one in Canada[26] and three in more than one country[5,9,27]. Gestational age at intervention varied within the second trimester. A total of 246 fetuses were included after exclusion of elective TOP, of which 112 were treated with VAS and 134 were managed conservatively. Characteristics of the included studies are summarized in Table 1.

Perinatal survival was reported in all selected studies. Sixty-four of the 112 fetuses in the VAS arm survived compared with 52 of the 134 fetuses in the conservative arm (57.1% *vs* 38.8%, $P < 0.01$). The pooled estimate of survival was different in the two arms, favoring VAS (OR, 2.54 (95% CI, 1.14–5.67)). Heterogeneity among studies was not significant (Q-test $P = 0.13$, $I^2 = 33\%$). On subgroup analysis among fetuses with non-favorable fetal urinary chemistry, the VAS arm yielded higher perinatal survival compared with the conservative arm (OR, 9.72 (95% CI, 1.89–50.09)). Improved perinatal survival in the VAS arm was less evident among fetuses with favorable fetal urinary chemistry (OR, 2.24 (95% CI, 0.89–5.67)). Heterogeneity in both analyses was absent among studies (Q-test $P = 0.96$ and $P = 0.98$, $I^2 = 0\%$). Forest plots for this analysis are illustrated in Figure 2.

Four studies provided information on postnatal survival 6–12 months after birth[5,9,22,27]. Survival was reported in 19 (44.2%) of the 43 fetuses treated with VAS and in 38 (41.8%) of the 91 fetuses managed conservatively. Pooled analysis did not reveal a significant difference (OR, 1.77 (95% CI, 0.25–12.71)). For this analysis, I^2 was 78% and Q-test *P*-value was 0.004 (Figure 3). Three studies provided 2-year follow-up of fetuses in both arms[5,22,27], including a total of 86 fetuses (30 treated with VAS *vs* 56 managed conservatively). Two-year survival was reported in 12 (40.0%) cases in the VAS arm and in 25 (44.6%) in the conservative arm. Pooled analysis of survival was not statistically significant (OR, 1.81 (95% CI, 0.09–38.03)). For this analysis, I^2 was 83% and Q-test *P*-value was 0.002 (Figure 4).

A subgroup analysis of five studies[5,9,21,25,27] that assessed postnatal renal function in both VAS and conservatively managed cases was conducted. The pooled OR of good postnatal renal function at 6 months to 2 years of age was higher in cases that had prenatal intervention with VAS, although the difference was not significant (OR, 2.09 (95% CI, 0.74–5.94), Q-test $P = 0.73$, $I^2 = 0\%$; Figure 5). Details of postnatal renal function among the included studies are given in Table 2.

According to quality assessment scores (Appendix S2), the quality of selected studies was satisfactory in most studies; the scores ranged from 4 to 7 of a total of 7 points. Prospective and more recent studies had generally higher scores. GRADE assessment for the quality of evidence for each outcome assessed ranged from moderate to very low.

DISCUSSION

This study demonstrates improvement in perinatal survival among fetuses with congenital LUTO that are treated with VAS. However, there was no evidence of improvement in survival and renal function at 6 months to 2 years among infants that had prenatal VAS.

Previous reviews suggested some improvement in perinatal survival with VAS. However, these reviews usually involved studies with small cohorts or case series that reported no survival advantage after excluding pregnancies with elective TOP or intrauterine fetal death. To avoid potential bias anticipated by previous systematic reviews[28], we excluded from the pooled analysis cases that underwent elective TOP. We included pregnancies with intrauterine fetal death since they could represent poor outcome of the natural disease process or intervention procedure. Fetal chromosomal abnormalities were excluded from all studies by either prenatal or postnatal karyotyping.

The survival advantage in the VAS group in our study is mainly attributed to its impact on fetal renal function and/or lung development; evidence supports that pulmonary hypoplasia could be fatal even after normalization of amniotic fluid following shunt placement. It is important to note that, while correction of oligohydramnios through VAS is expected to prevent pulmonary morbidities, it has been reported that oligohydramnios

Table 1 Characteristics of studies comparing perinatal outcome in fetuses with lower urinary tract obstruction treated with vesicoamniotic shunt (VAS) or conservative management (CM) included in systematic review

Study	*Country*	*Study design*	*Study period*	*Sample size (n)**	*GA at VAS (weeks)*	*Diagnosed anomaly†*	*Prognosis prior to VAS*	*Urine biochemistry criteria for poor renal function*	*GA at delivery (weeks)*
Morris (2015)[27]	UK; The Netherlands	Prosp	Aug 2006 to Dec 2010	39	NS	VAS: 2 PUV, 1 urethral atresia CM: 16 PUV, 1 urethral atresia	Severe bilateral hydronephrosis in 1 (10%) VAS and 4 (11%) CM; severe renal pelvic dilation in 5 (50%) VAS and 19 (54%) CM	NA	NS
Ruano (2015)[9]	Brazil; France	Retro	Jan 1990 to Aug 2013	48	20.2 ± 3.9	VAS: 15 PUV, 3 vesicoureteral reflux, 2 urethral atresia, 1 prune belly syndrome, 1 megalourethra‡	Both groups had favorable prognosis based on fetal urinary chemistry; urinary Na, Ca and Cl levels comparable	Na < 100 mEq/L, Cl < 90 mEq/L, osmolarity < 210 mOsm/L, β2 microglobulin < 6 mg/dL in latest sample of maximum 3 samples	25.1 ± 7.9 *vs* 27.3 ± 8.2§
Morris (2013)[5]	UK; Ireland; The Netherlands	RCT	Oct 2006 to Sep 2012	26	NS	VAS: 5 PUV, 4 urethral atresia CM: 4 PUV, 1 urethral atresia, 1 urethral stenosis causing obstruction	Severe bilateral hydronephrosis in 1 (6.25%) VAS and 0 CM; severe renal pelvic dilation in 13 (81.25%) VAS and 12 (80%) CM	NA	35.6 *vs* 36.4§
McLorie (2001)[26]	Canada	Retro	1989–1998	9	20–28	4 PUV, 1 urethral atresia, 1 prune belly variant and urethral atresia (6 fetuses survived)	Fetuses with good prognosis selected for VAS (based on renal chemistry)	Ca < 2 mmol/L, Na < 100 mmol/L, Cl < 90 mmol/L, osmolarity < 200 mOsm/L, β2 microglobulin < 508 mmol/L, total protein < 0.2 g/L (2 bladder taps per patient)	31–36
Freedman (1996)[25]	USA	Retro	1987–1994	42	NS	13 PUV, 11 urethral atresia, 9 prune belly syndrome, 4 cloacal dysgenesis, 6 miscellaneous anomalies, otherwise unknown or autopsy declined	Good prognosis in 79% of VAS *vs* 41% of CM	Na < 100 mEq/L, osmolarity < 200 mOsm/L	NS
Johnson (1994)[24]	USA multicenter study	Retro and prosp	NS	11	14–24	3 PUV, 1 cloacal anomaly, 1 megaurethra– anterior urethral valves, 1 megacystis– microcolon syndrome, 3 urethral atresia, 5 prune belly syndrome	VAS: 40% poor renal function *vs* 60% good renal function	Na < 100 mg/dL, Ca < 8 mg/dL, osmolarity < 200 mOsm/L, β2 microglobulin < 4 mg/dL, total protein < 40 mg/dL (minimum 3 bladder taps at 48–72 h)	NS
Lipitz (1993)[23]	UK	NS	NS	19	19–25	PUV	NS	NA	NS
Nicolini (1991)[22]	UK	NS	NS	13	17–28	NS	NS	NA	30–39
Crombleholme (1990)[21]	USA	Retro	1 Jan 1981 to 14 May 1988	39	NS	NS	60% poor renal function *vs* 40% good renal function	Na < 100 mEq/L, Cl < 90 mEq/L, osmolarity < 200 mOsm/L	NS

Only first author given for each study. *Cases of elective termination of pregnancy (TOP) excluded. †Prenatal or postnatal diagnosis. ‡Discrepancies between sample size and other numbers attributed to number of fetuses excluded for elective TOP. §VAS *vs* CM. Ca, calcium; Cl, chloride; GA, gestational age; Na, sodium; NA, not applicable; NS, not specified; Prosp, prospective; PUV, posterior urethral valves; RCT, randomized controlled trial; Retro, retrospective.

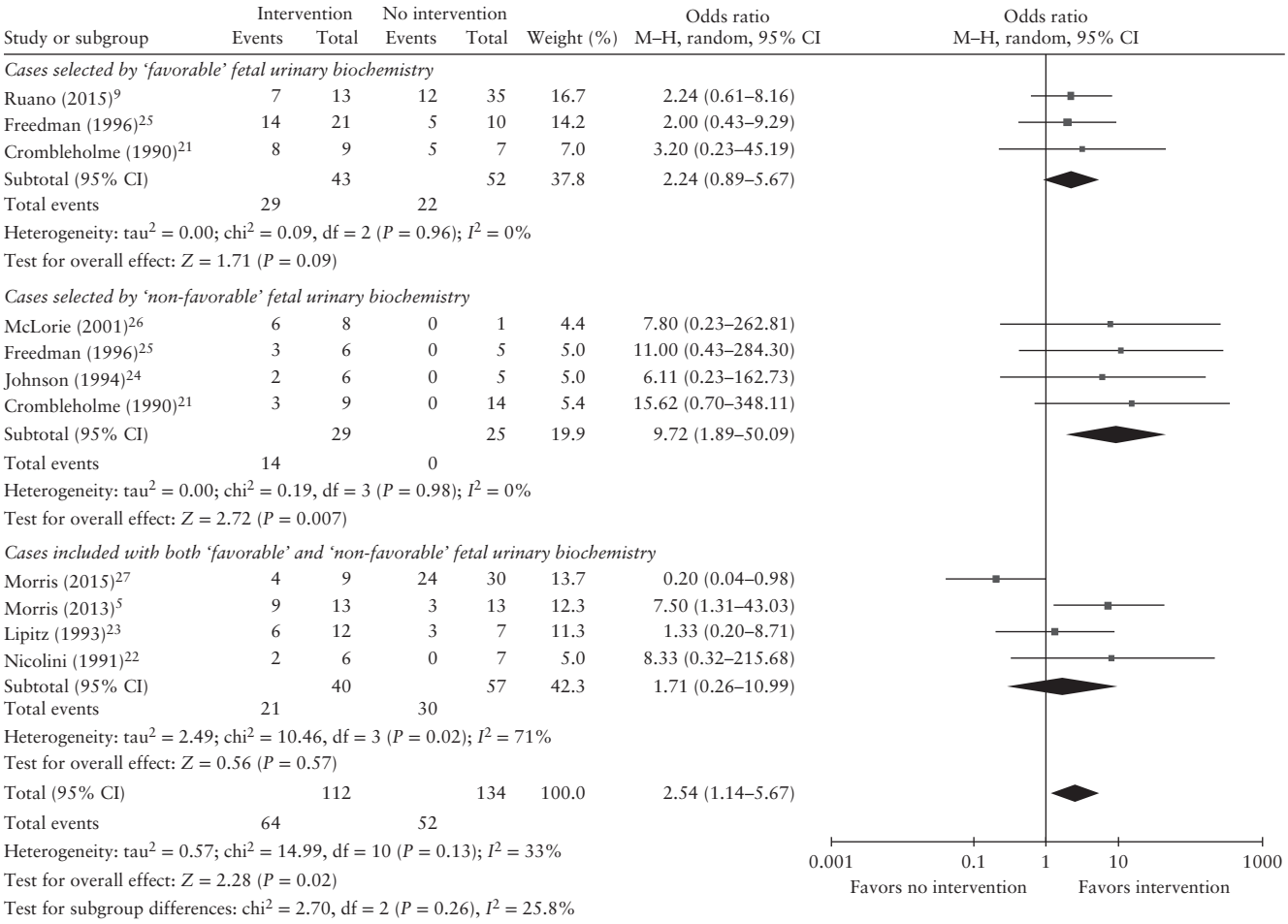

Figure 2 Forest plot of perinatal survival in fetuses with lower urinary tract obstruction treated with vesicoamniotic shunt (intervention) or conservative management (no intervention), categorized according to prognosis based on fetal urinary biochemistry. M–H, Mantel–Haenszel.

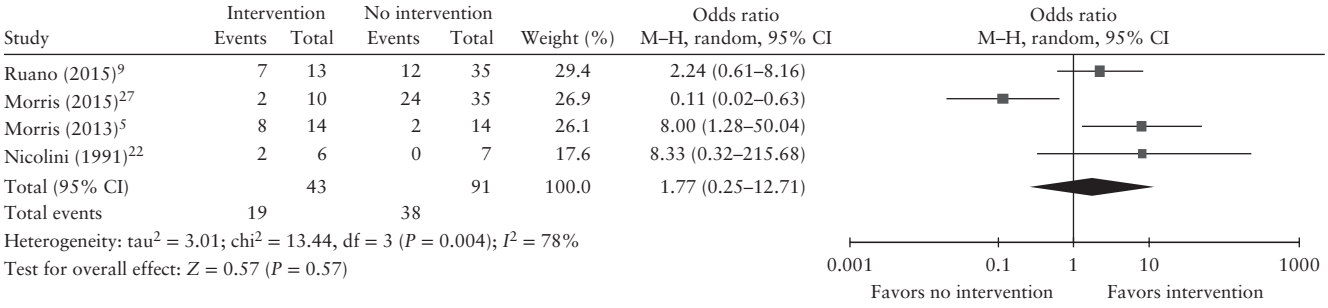

Figure 3 Forest plot of postnatal survival at 6–12 months of age in fetuses with lower urinary tract obstruction treated with vesicoamniotic shunt (intervention) or conservative management (no intervention). M–H, Mantel–Haenszel.

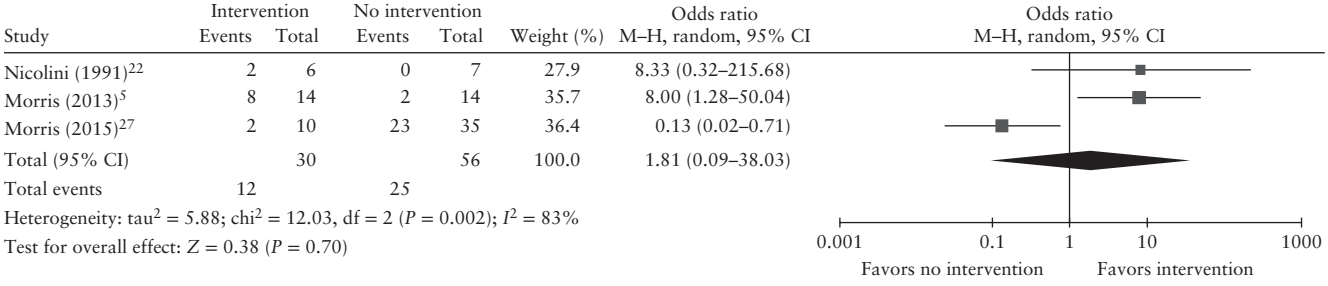

Figure 4 Forest plot of postnatal survival at 2 years of age in fetuses with lower urinary tract obstruction treated with vesicoamniotic shunt (intervention) or conservative management (no intervention). M–H, Mantel–Haenszel.

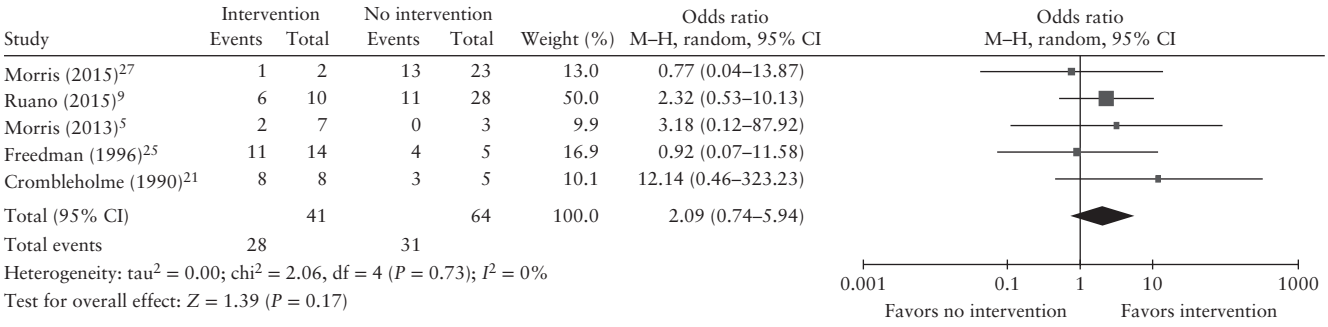

Figure 5 Forest plot of good postnatal renal function in fetuses with lower urinary tract obstruction treated with vesicoamniotic shunt (intervention) or conservative management (no intervention). M–H, Mantel–Haenszel.

complicating pregnancy during the critical period of 16–24 weeks of gestation (canalicular phase) may cause irreversible pulmonary hypoplasia[29]. The VAS design and procedure of insertion is not without risks, and complications have been reported in a significant number of cases (Table 3).

Several sonographic and biochemical (urine analytes) parameters have been used to evaluate fetal renal function and, consequently, to select adequate candidates for fetal intervention. However, none of the ultrasound parameters has been proven to be highly sensitive[4]. Moreover, considering normal amniotic fluid as an exclusion criterion for VAS placement has been challenged by the fact that some cases develop renal failure later in gestation or postnatally. A meta-analysis that evaluated the utility of urine analytes for prediction of poor renal function demonstrated limited clinical accuracy[30]. Therefore, a combination of fetal urinary biochemistry and ultrasound evaluation of fetal renal parameters (fetal renal cortical cysts, echogenicity or signs of renal dysplasia), as well as amniotic fluid assessment, could be used to select fetuses that would benefit most from intrauterine VAS placement.

The main strength of this meta-analysis is the inclusion of a randomized controlled trial and recent studies that included relatively large cohorts, as opposed to the small studies in earlier reviews. This analysis also excluded cases of elective TOP that could be a potential source of bias in previous reports. In addition, the present systematic review provides new information to the current literature as we evaluated the effectiveness of VAS considering the estimated fetal renal function at the time of indication for the procedure. Our results suggest that cases with poor prognostic features may still benefit from VAS since the mortality rate without fetal intervention is extremely high due to severe pulmonary hypoplasia. This fact indicates that further prospective studies are necessary to confirm the benefits according to the severity of LUTO. Recently, Ruano *et al.* proposed a new classification of LUTO based on the severity and estimated renal function (Stages I–III), which may be useful to guide further studies in the evaluation of the effectiveness of fetal therapy in LUTO[31].

Another aspect that is unique to the present systematic review is that only confirmed LUTO cases were included in the analysis, i.e. fetuses with confirmed enlarged bladder associated with bilateral hydronephrosis. Previous systematic reviews included cases with unilateral hydronephrosis, which does not meet the definition for LUTO[10]. We also reported survival rates up to 2 years of age.

The main limitation of this systematic review is that all of the included studies, except one, were not randomized trials. Unfortunately, performing a randomized controlled trial with a large sample size to evaluate the effectiveness of VAS for LUTO is extremely challenging because of difficulties in recruitment, ethical concerns, low frequency of the disease and the large spectrum of prognosis[3,5]. Non-randomized studies can create severe bias of selection and clinical interpretation, for example, if the non-treated group has less severe LUTO than the treated group, the study could give the false impression that VAS is associated with worse outcome than is prenatal expectant management[25].

A further limitation is the lack of consistency in fetal selection criteria for intervention or conservative management. Estimation of postnatal renal function in both groups was not feasible in all studies as data were either lacking or reported inconsistently, particularly in terms of time of assessment. In addition, another difficulty in evaluating the effectiveness of fetal therapy for LUTO is that studies usually consider different methods to define normal/abnormal renal function (Table 2). It is recommended, for future studies, to standardize the method for evaluation of postnatal renal function using the Schwartz formula to estimate the glomerular filtration rate in the infant[32]. Finally, due to the lack of strong evidence from included studies (quality of evidence ranged from moderate to very low according to GRADE guidelines)[33], the findings of this review should be interpreted with caution until appropriate-level evidence from adequate multicenter randomized controlled trials is available.

A consideration when evaluating fetal VAS for LUTO is cost-effectiveness. It has been reported that VAS is not a cost-effective procedure as it can improve survival without preventing perinatal morbidity[34]. However, these findings were based on a cost-analysis model of a single study in which no selection criteria based on the severity of LUTO were considered (some fetuses already had abnormal

Table 2 Postnatal assessment of renal function after delivery in fetuses with vesicoamniotic shunt (VAS) or conservative management (CM) for lower urinary tract obstruction

Study	Age at assessment	Normal renal function/survivors (n/N)		Method of assessment
		VAS	CM	
Ruano (2015)[9]	6 months	6/10	11/28	Serum creatinine (normal renal function: < 50 µmol/L ± 2 SD on average of last 5 samples) and need for dialysis
Morris (2015)[27]	28 days	1/7	9/24	Serum creatinine (normal renal function: < 50 µmol/L), renal ultrasound appearance and need for medical treatment, dialysis or transplantation
	1 year	1/3	12/24	
	2 years	1/2	13/23	
Morris (2013)[5]	28 days	2/8	0/4	Serum creatinine (normal renal function: < 50 µmol/L), renal ultrasound appearance and need for medical treatment, dialysis or transplantation
	1 year	2/7	0/3	
	2 years	2/7	0/3	
Crombleholme (1990)[21]				Serum creatinine (normal renal function: < 0.3 mg/dL)
Poor prognosis	16 months	1/3	0/0	
Good prognosis	NS	8/8	3/5	
Johnson (1994)[24]				Serum creatinine (good outcome: ≤ 1.0 mg/dL at 1 year)
Poor prognosis	2 years	0/2	0/0	
Good prognosis	2 years	6/6	3/3*	
Freedman (1996)[25]				Serum creatinine (renal failure: < 2 SD above adjusted normal mean), development of CRF and need for renal replacement therapy
Poor prognosis	NS	1/3	0/0	
Good prognosis	NS	11/14	4/5	
McLorie (2001)[26]				Creatinine clearance calculated by Shwartz equation (normal renal function: > 70 mL/min), need for renal replacement therapy, dialysis or renal transplantation
Good prognosis	NS	3/6	0/0	
Nicolini (1991)[22]	NS	2/2	0/0	NS
Lipitz (1993)[23]	NS	1/6	0/0	GFR (renal impairment: below expected for age and weight), serum creatinine (renal impairment: > 70 mmol/L after first week of age), dimercaptosuccinic acid scan (renal impairment: < 40% differential function and decreased uptake) and need for dialysis

Only first author given for each study. *Obstruction resolved after vesicocentesis. CRF, chronic renal failure; GFR, glomerular filtration rate; NS, not specified.

Table 3 Complications of vesicoamniotic shunt (VAS) reported in the literature

Study	Spontaneous ROM	Miscarriage following shunt insertion	Dislodgment of shunt	Blockage of shunt	Chorio-amnionitis	Bladder rupture following shunt insertion	Failed shunt insertion
Morris (2015)[27]	3/10 (30)	1/10 (10)	4/10 (40)	2/10 (20)			
Morris (2013)[5]	3/15 (20)		3/15 (20)	1/15 (6.7)			
Ruano (2015)[9]			5/16 (31.3)*				
Anumba (2005)[1]	1/5 (20)						1/5 (20)
McLorie (2001)[26]			2/9 (22.2)			1/9 (11.1)	
Freedman (1996)[25]			1/28 (3.6)		1/28 (3.6)		
Johnson (1994)[24]		2/15 (13.3), 1 week after procedure	9/15 (60): 6 displaced into amniotic space, 3 displaced intraperi-toneally				
Lipitz (1993)[23]		1/12 (8.3), 7 days after procedure					
Nicolini (1991)[22]		1/8 (12.5) with signs of chorioam-nionitis					
Crombleholme (1990)[21]					3/19 (15.8)		
Wilkins (1987)[35]				1/2 (50)			1/2 (50)

Data are given as *n*/*N* (%). *Includes cases of dislodgment or blockage of shunt. ROM, rupture of membranes.

renal function before shunt placement). In addition, the cost-effectiveness of fetal therapy for LUTO needs to be investigated on the basis of long-term survival, initially, and then morbidity, including long-term outcomes of pediatric dialysis and renal transplant.

ACKNOWLEDGMENT

We thank Larry J. Prokop, the expert librarian, for his contribution and effort throughout the search process.

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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 and meta-analysis.

Appendix S2 Assessment of risk of bias and quality of evidence.