European Journal of Obstetrics & Gynecology and Reproductive Biology 233 (2019) 120–126

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Outcomes in fetuses diagnosed with megacystis: Systematic review and meta-analysis

Lizhu Chen[a], Johnny Guan[b], Hui Gu[c], Mo Zhang[d,*]

[a] Department of Ultrasound, Shengjing Hospital, China Medical University, Shenyang, China
[b] Department of Urology, University of California Los Angeles, Los Angeles, CA, USA
[c] Key Laboratory of Health Ministry for Congenital Malformation, Shengjing Hospital, China Medical University, Shenyang, China
[d] Department of Urology, Shengjing Hospital, China Medical University, No. 36 Sanhao Street, Heping District, Shenyang, Liaoning 110004, China

ARTICLE INFO

Article history:
Received 6 August 2018
Received in revised form 25 November 2018
Accepted 3 December 2018

Keywords:
Megacystis
Prenatal diagnosis
Outcome

ABSTRACT

Objective: To explore the outcomes and prognostic factors associated with fetal megacystis (enlarged bladder).
Study design: The MEDLINE and EMBASE databases were searched for studies reporting on outcomes of fetal megacystis. The outcomes observed were chromosomal abnormalities, associated structural anomalies, spontaneous resolution, and survival rates. We also evaluated the potential role of fetal gender, oligohydramnios, gestational age at diagnosis, and intrauterine intervention as prenatal prognostic factors.
Results: The search identified 558 articles in total, and 13 studies (1675 fetuses) were included in this systematic review. The overall incidences of chromosomal abnormalities and associated structural anomalies in fetal megacystis were 10% and 24%, respectively. Spontaneous resolution of megacystis occurred in 32% of fetuses, and 44% of fetuses were born alive and survived until the follow-up. The odds ratio of survival with oligohydramnios was 0.14, and the mean difference in gestational age at diagnosis between survival and non-survival was 3.43 weeks. No significant difference in survival rate was observed between the genders, and an intrauterine intervention did not significantly improve the prognosis.
Conclusions: A considerable proportion of fetuses with megacystis are born with a good prognosis. Oligohydramnios and lower gestational age at diagnosis are associated with worse outcomes.
© 2018 Elsevier B.V. All rights reserved.

Contents

* Corresponding author.
E-mail address: zhangmo@sj-hospital.org (M. Zhang).

https://doi.org/10.1016/j.ejogrb.2018.12.007
0301-2115/© 2018 Elsevier B.V. All rights reserved.

Introduction

Fetal megacystis is an ultrasonic manifestation, revealed as an enlarged bladder after 10 weeks of gestation [1]. It is more common in males, and usually implies a mechanical or functional bladder outlet obstruction. The most common cause in boys is posterior urethral valves, whereas the cause is urethral atresia in females [2]. Fetal megacystis can be accompanied by some chromosomal abnormalities and other associated structural abnormalities.

The diagnostic criteria for fetal megacystis vary in different studies. Fetal megacystis is usually defined as a longitudinal bladder diameter $\geq$7 mm in the first trimester, and as an enlarged bladder failing to empty in 45 min in the second and third trimesters. Fetuses with megacystis are generally believed to have poor prognoses, as megacystis is often associated with severe oligohydramnios, renal failure, and pulmonary hypoplasia [3–6]. Thus, many parents choose to terminate the pregnancy after the diagnosis. However, as some previous studies have reported, not all fetuses with megacystis warrant termination. Fetuses with isolated fetal megacystis may resolve spontaneously, and some fetuses can be born alive with good prognoses. In addition, intrauterine therapy is performed occasionally, but whether it can improve neonatal outcomes needs to be established.

Above all, antenatal counseling in cases of fetal megacysits remains a clinical dilemma. Perinatal survival rates in cases of megacysits are not well known, and prenatal prognostic factors need to be defined. Therefore, this study aims to assist clinicians with prenatal counseling by investigating the prognosis and prognostic factors in megacystis that may predict perinatal outcomes.

Methods

Protocol, eligibility criteria, information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The MEDLINE and EMBASE databases were searched electronically using keywords and word variants for “megacystis”, “prenatal diagnosis” and “outcome” on 12 February 2018 (Table S1).

Study selection and data collection

Studies describing the perinatal outcome of fetuses with megacystis were included. All titles and abstracts were reviewed independently by two authors (L.C. and M.Z.), and related articles in the references were searched manually for additional records. The same two authors also worked independently to review the full text of articles and extract the relevant data. Any inconsistencies were resolved by discussion. If more than one article had been published using the same population, the study containing the most comprehensive information was included. The final search was restricted to the English language published after the year 2000, and all duplications were removed. Only original research articles were considered eligible for inclusion, and case reports and reviews were excluded. The quality assessment was conducted using the Newcastle–Ottawa Scale (NOS).

Synthesis of results

The incidence of the following outcomes was analyzed in fetuses with megacystis: chromosomal abnormalities, associated structural anomalies, spontaneous resolution of megacystis, and survival rates. In addition, we evaluated the potential role of fetal gender, oligohydramnios, gestational age at diagnosis, and intrauterine intervention as prenatal prognostic factors. Cases that underwent prenatal intervention (vesicocentesis and vesicoamniotic shunt) were analyzed separately and were not included with the other studies.

Statistical analysis

Meta-analyses of proportions were used to combine data and quantify the incidence rates of the perinatal outcomes. Data were expressed as odds ratios (OR) and 95% confidence interval (CI) to analyze the prognostic factors. Forest plots were constructed for each study. Statistically significant heterogeneity was considered if the inconsistency square (I^2) was >50% or if the Cochran Q test revealed $P < 0.10$. A random-effect model was applied when there was significant heterogeneity. Data were analyzed using Stata version 13.1 software (2013; Stata Corp., College Station, TX, USA).

Results

Study selection and quality assessment

A total of 558 articles were identified, and 55 were assessed for their eligibility of inclusion. Forty-two articles were excluded because they did not contain the outcomes from megacystis, because they had overlapping populations, or because we could not extract primary data from the articles. Finally, 13 studies including 1675 fetuses with megacystis were included in this meta-analysis (Table 1) [5,7–18]. The flowchart of study selection is outlined in Fig. 1.

The NOS was applied to the cohort studies to assess the quality of the included studies (Table 2). Most of the studies showed overall good quality with regard to selection and comparability of the study groups and ascertainment of the outcomes of interest. The main weaknesses of these studies were their retrospective design, and some studies did not report on all outcomes included in the systematic review.

Synthesis of results

Chromosomal abnormalities and associated structural abnormalities

The incidence rates of chromosomal abnormalities were evaluated in ten studies including 1088 fetuses prenatally diagnosed with megacystis. The overall incidence of chromosomal abnormalities was 10% (95% CI, 6%–14%). Eight studies including 1312 fetuses evaluated the associated structural abnormalities, and the overall incidence was 24% (95% CI, 16%–31%) (Fig. 2).

Spontaneous resolution of megacystis

Seven studies including 458 fetuses evaluated the incidence of spontaneous resolution. Cases that underwent an intrauterine intervention were excluded. The overall incidence of spontaneous

Table 1
Characteristics of studies on fetuses with prenatally diagnosed megacystis included in the systematic review.

Study	Population	Study design	Year	Cases	Prevalence	Male	GA at diagnosis	Time at follow-up
Iuculano et al. [7]	Italy	Retro	2018	26	NS	87.0%	11w–13w	NS
Taghavi et al. [8]	New Zealand	Retro	2017	16	0.11%	81.3%	11w–32w	5.3years
Fontanella et al. [9]	Netherlands	Retro	2017	541	NS	NS	11w–36w	NS
Pellegrino et al. [10]	Italy	Retro	2017	25	0.4%	76%	12w-34w	29months
Lee et al. [5]	Australia	Retro	2017	61	NS	85.2%	11w–39w	NS
Tschannen et al. [11]	Switzerland	Retro	2017	53	0.2%	NS	13w–35w	2–12 years
Girard et al. [12]	France	Retro	2016	5	NS	NS	11w–12w	NS
Fievet et al. [13]	France	Retro	2014	69	0.38%	82.6%	11w–35w	2years
Müller et al. [14]	Switzerland	Retro	2014	54	NS	83.3%	10w–39w	7.8years
Bornes et al. [15]	France	Retro	2013	84	NS	79.7%	11w–35w	1year
Al-Hazmi et al. [16]	France	Retro	2012	561	NS	86.6%	12w–36w	2years
Kagan et al. [17]	UK	Retro	2010	35	NS	NS	11w–13w	NS
Liao et al. [18]	UK	Retro	2003	145	NS	93.1%	10w–14w	NS

GA gestational age, *Retro* retrospective, *NS* not stated, *w* weeks.

resolution of megacystis was 32% (95% CI, 19%–44%). Significant heterogeneity was observed among the studies ($I^2 = 85.5\%$, $P < 0.001$). We divided the cases into two subgroups according to the gestational age at diagnosis. Cases diagnosed before 18 weeks were defined as early megacystis, whereas all cases diagnosed after 18 weeks were defined as late megacystis. The early megacystis group yielded a higher incidence of spontaneous resolution [40% (95% CI, 33%–46%)] compared to the late megacystis group [12% (95% CI, 8%–17%)]. Heterogeneity was not significant in either subgroup analysis (early megacystis group, $I^2 = 8.1\%$, $P = 0.366$; late megacystis group, $I^2 = 0.0\%$, $P = 0.745$) (Fig. 3).

Perinatal survival

Ten studies including 1031 fetuses explored the survival rates of fetuses with megacystis. Overall, 44% (95% CI, 33%–54%) of fetuses were born alive and survived until follow-up. Significant heterogeneity was observed among the studies ($I^2 = 81.2\%$, $P < 0.001$), which may have been caused by the different durations of follow-up (Fig. 4).

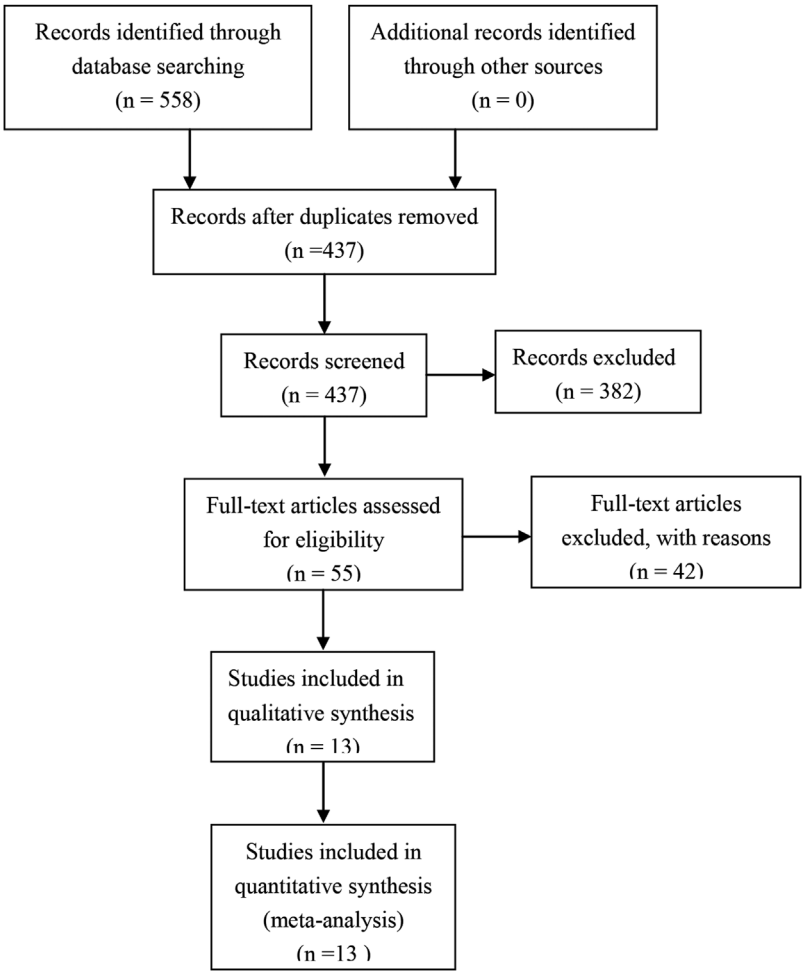

Fig. 1. Flow diagram of included studies in systemic review.

Table 2
Quality assessment of the 13 included studies according to the Newcastle–Ottawa Scale.

Study	Selection	Comparability	Outcome
Iuculano et al. [7]	★★	★★	★★
Taghavi et al. [8]	★★★	★	★★★
Fontanella et al. [9]	★★★	★★	★★
Pellegrino et al. [10]	★★	★	★★★
Lee et al. [5]	★★★	★	★
Tschannen et al. [11]	★★★	★	★★
Girard et al. [12]	★	★	★★
Fievet et al. [13]	★★★	★★	★★
Müller et al. [14]	★★	★	★★★
Bornes et al. [15]	★★★	★	★★
Al-Hazmi et al. [16]	★★★	★	★★
Kagan et al. [17]	★★	★	★
Liao et al. [18]	★★	★	★★

Fetal gender

Seven studies assessed the ability of fetal gender to predict survival. Overall, the OR of survival with a male fetus was 0.70 (95% CI, 0.28–1.76). No significant difference in survival rates was observed between male and female fetuses (overall effect = 0.75, P = 0.45). Heterogeneity among these studies was not significant (I^2 = 23.7%, P = 0.25) (Fig. 5A).

Oligohydramnios

Five studies assessed the performance of oligohydramnios in predicting survival. Overall, the OR of survival with oligohydramnios was 0.14 (95% CI, 0.15–0.37). There was a significant difference in survival rates between fetuses with oligohydramnios and fetuses with normal amniotic fluid (overall effect = 3.93, P < 0.001). Heterogeneity among these studies was not significant (I^2 = 0.0%, P = 0.48). (Fig. 5B)

Gestational age at diagnosis

Four studies assessed the difference in mean gestational age at diagnosis between survivors and nonsurvivors. The mean difference in gestational age at diagnosis between survival and nonsurvival was 3.43 (95% CI, 0.84–6.01) weeks (overall effect = 2.60, P = 0.009). Heterogeneity among these studies was not significant (I^2 = 0.0%, P = 0.71) (Fig. 5C).

Intrauterine intervention

Six studies assessed perinatal survival in both intrauterine interventional cases and conservative cases. They included 94 fetuses

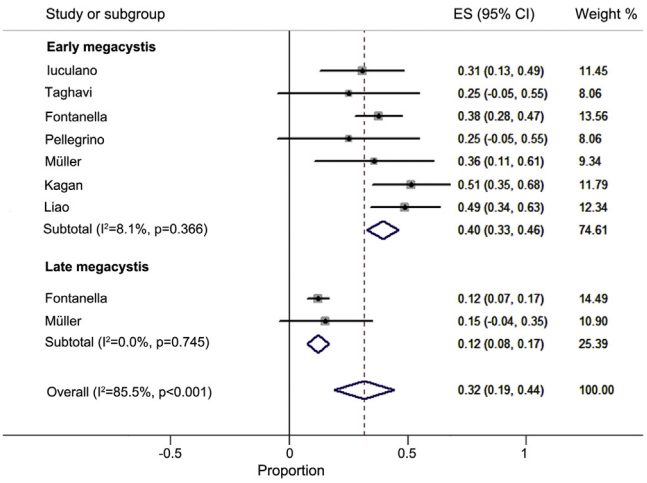

Fig. 3. Pooled proportions for spontaneous resolution of megacystis.

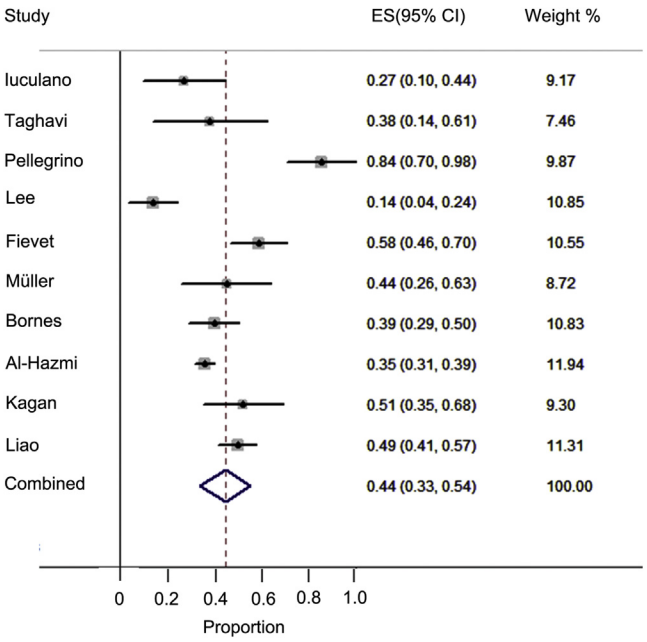

Fig. 4. The overall survival rate of fetuses with megacystis.

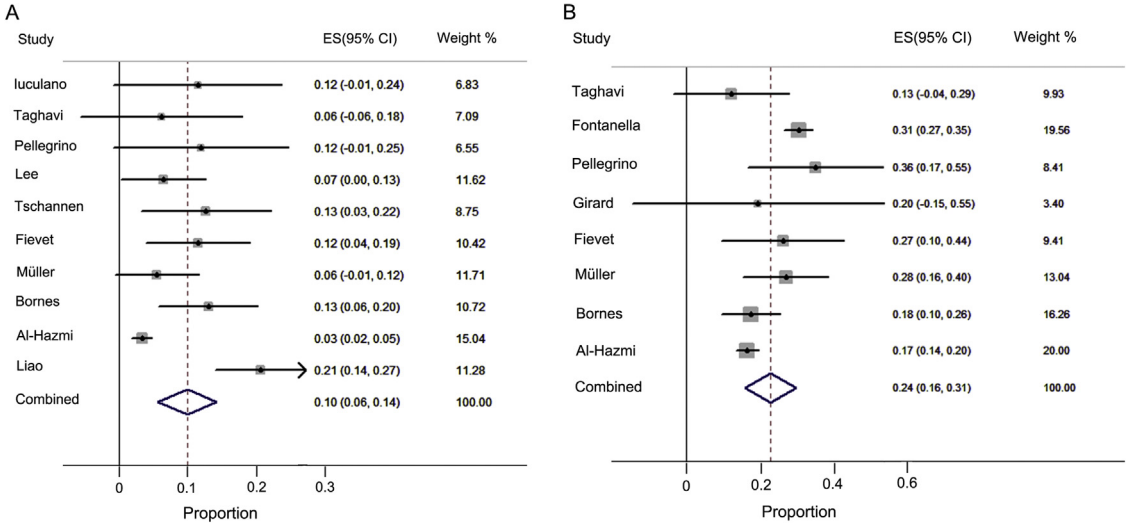

Fig. 2. Pooled proportions for chromosomal abnormalities (A) and associated structural anomalies (B) in fetuses with megacystis.

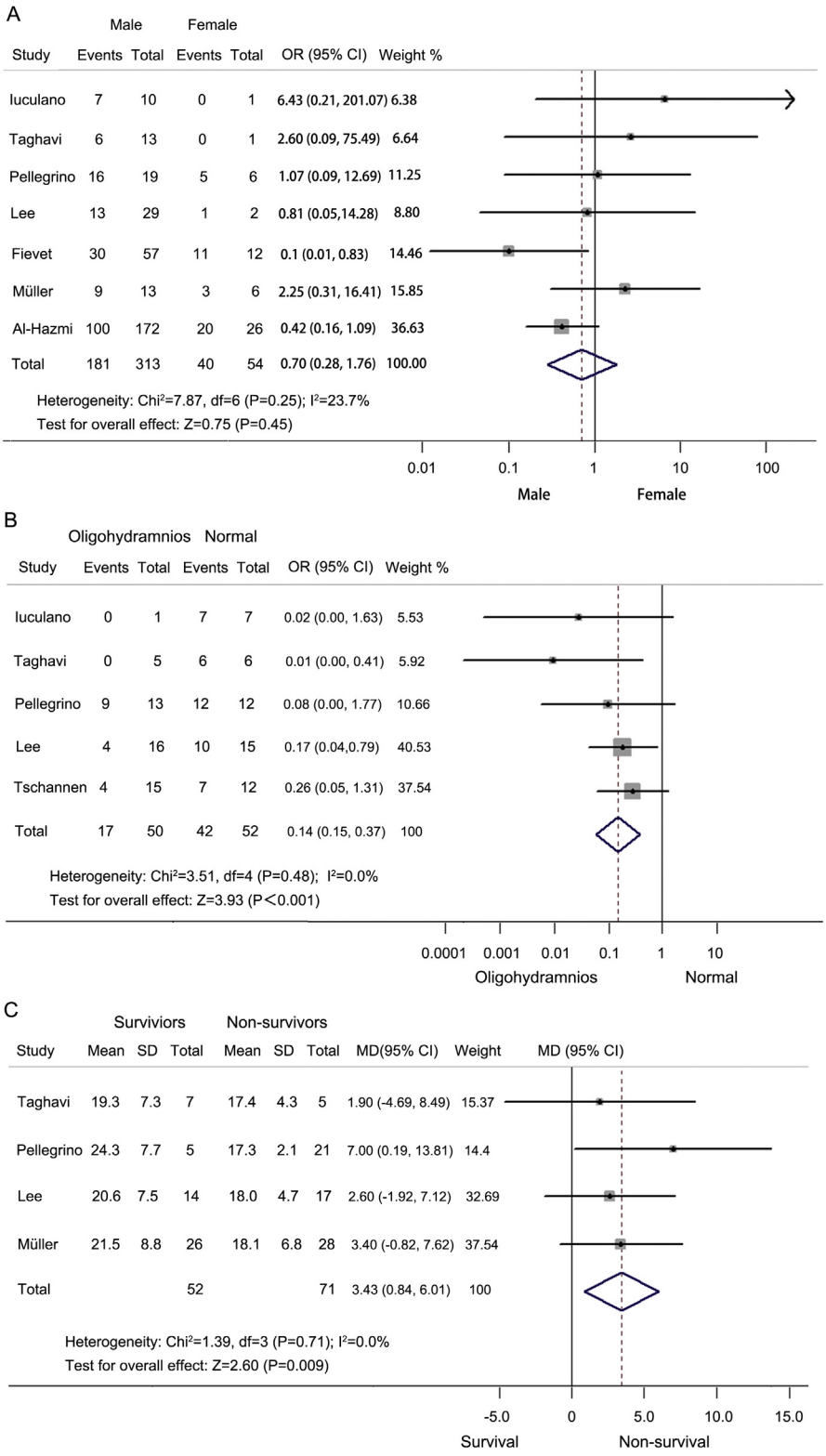

Fig. 5. (A) Odds of survival in male and femal fetuses. (B) Odds of survival if oligohydramnios. (C) Mean difference in gestational age at diagnosis of survivors and non-survivors.

who received prenatal intervention (vesicocentesis and/or vesicoamniotic shunt) and 74 fetuses who received no treatment. Overall, the OR of survival after intrauterine intervention was 0.61 (95% CI, 0.29–1.29). No significant difference was observed between these two groups (overall effect = 1.29, P = 0.20). Heterogeneity between these studies was not significant (I^2 = 0.0%, P = 0.96) (Fig. 6).

Discussion

The prevalence of megacystis in the studies was reported to be 0.11%–0.40%. Individual outcomes were highly variable among the studies; thus, prenatal counseling in cases of fetal megacysits remains a clinical dilemma. To our knowledge, this is the most

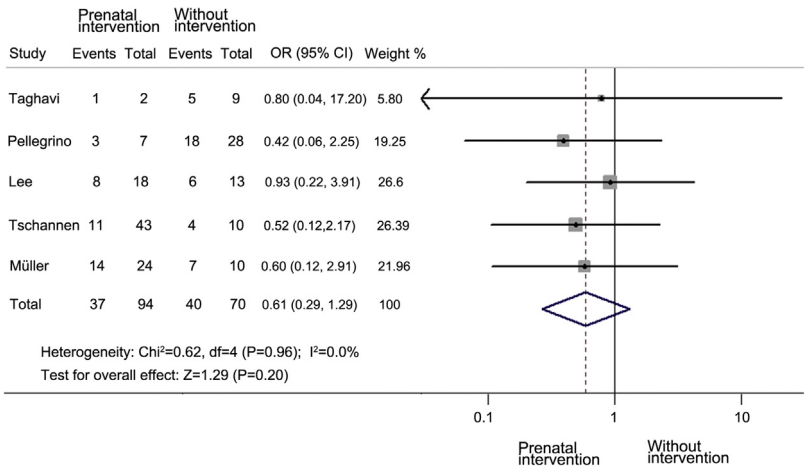

Fig. 6. Survival rates with and without intervention.

comprehensive systematic review and meta-analysis investigating the outcomes and prognostic factors in megacystis.

Our review showed a strong correlation between megacystis and chromosomal or other associated structural abnormalities. The most common chromosomal abnormalities were Trisomy 13, Trisomy 18, and Trisomy 21. Other associated structural malformations mainly included anorectal malformation, Prune-belly syndrome, caudal dysgenesis, megacystis-microcolon-intestinal hypoperistalsis syndrome, cloacal malformation, and intestinal malformation. Therefore, fetal karyotyping is recommended when megacystis is diagnosed, and a thorough ultrasound examination should be performed to rule out other associated anomalies.

Fetuses with megacystis are generally believed to have poor prognoses. In China, most parents choose to terminate the pregnancy after clinical counseling. Our results revealed that more than 30% of cases of megacystis resolved spontaneously *in utero*. Particularly, spontaneous resolution occurred in nearly 40% of cases diagnosed before 18 weeks. However, only 12% of cases diagnosed after 18 weeks resolved spontaneously. This result suggests that more than one-third of megacystis cases diagnosed before 18 weeks are self-limiting and require observation. In contrast, the outcomes of megacystis diagnosed after 18 weeks are largely uncertain.

According to our study, more than 40% of fetuses were born alive and survived until follow-up. Notwithstanding inconsistencies among studies that have explored survival of megacystis, there is sufficient evidence to suggest that a considerable proportion of fetuses could survive perinatally. However, there is a definite need for an objective and consistent method to evaluate the survival rates of megacystis. The details of fetal outcomes including renal function should be included, and the lengths of the follow-up period should be fixed.

Our review also assessed the impact of factors, such as fetal gender, oligohydramnios, and gestational age at diagnosis, on fetal outcome. We found that fetal gender did not predict outcome, whereas oligohydramnios and gestational age at diagnosis were superior in their ability to predict survival. Megacystis fetuses with normal amniotic fluid volume have a much better prognosis. The volume of amniotic fluid is a reflection of renal function. The risk of renal dysplasia and subsequent lung hypoplasia is high in cases of oligohydramnios [19–21]. Therefore, fetuses with oligohydramnios are usually accompanied by a poor prognosis. Our study also found a significant difference between gestational age at diagnosis of survivors versus nonsurvivors. Increased gestational age at diagnosis was correlated with an increased survival rate, which may be caused by different etiologies at different time points. Posterior urethral valves (PUV) is the most common etiology in the second and third trimesters, and PUV diagnosed in the third trimester are reported to be less obstructive with a better outcome [22].

The role of intrauterine intervention is also controversial [23]. Vesicocentesis and vesicoamniotic shunt are the most common prenatal interventional methods, and a urinary obstruction can be relieved temporarily using these methods. However, their effects on long-term survival and renal function remain uncertain [24–26]. Our systemic analysis included six studies (168 fetuses), and found no significant differences in survival rates between the interventional cases and conservative cases. However, most of the time, cases in the interventional group were more serious than cases in the conservative group; thus, the results from this systematic review may have overestimated the adverse outcomes associated with intrauterine intervention. In addition, due to the different gestational ages at intervention, lengths of follow-up, and lack of well recognized indications, the evaluation of the effect of intrauterine therapy was also considerably biased. Therefore, a well-designed randomized control study is needed to ascertain the value of intrauterine intervention.

The limitations of our meta-analysis included the retrospective design of all studies, different lengths of follow-up, and that some of the observed outcomes were reported in only a limited number of the included articles. Furthermore, because of the paucity of raw data, we could not assess the ability of bladder size to predict survival. Despite these limitations, this review still represents the most comprehensive published estimate of the investigated outcomes and prognostic factors in fetuses with megacystis.

In conclusion, megacystis is commonly associated with chromosomal abnormalities and other structural abnormalities. More than 30% of cases with megacystis resolved spontaneously, suggesting the necessity for serial follow-up examinations during pregnancy. Not all fetuses with megacystis warrant termination, as a considerable proportion of fetuses survive perinatally. Oligohydramnios and gestational age at diagnosis are the major determinants of perinatal outcome. Future randomized trials are needed to assess the role of intrauterine intervention in the management of megacystis.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant 81600258) and the National Natural Science Foundation of Liaoning Province (Grant 20170541002).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2018.12.007.

References

[1] McHugo J, Whittle M. Enlarged fetal bladders: aetiology, management and outcome. Prenat Diag 2001;21:958–63.
[2] Stadie R, Strizek B, Gottschalk I, Geipel A, Gembruch U, Berg C. Intrauterine vesicoamniotic shunting for fetal megacystis. Arch Gynecol Obstet 2016;294:1175–82.
[3] Morris RK, Middleton LJ, Malin GL, Quinlan-Jones E, Daniels J, Khan KS, et al. Outcome in fetal lower urinary tract obstruction: a prospective registry study. Ultrasound Obstet Gynecol 2015;46:424–31.
[4] Jouannic JM, Hyett JA, Pandya PP, Gulbis B, Rodeck CH, Jauniaux E. Perinatal outcome in fetuses with megacystis in the first half of pregnancy. Prenat Diag 2003;23:340–4.
[5] Lee J, Kimber C, Shekleton P, Cheng W. Prognostic factors of severe foetal megacystis. ANZ J Surg 2011;81:552–5.
[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 Diag 2005;25:7–13.
[7] Iuculano A, Peddes C, Monni G. Early fetal megacystis: is it possible to predict the prognosis in the first trimester? J Perinat Med 2018(January (24)).
[8] Taghavi K, Sharpe C, Stringer MD, Zuccollo J, Marlow J. Fetal megacystis: institutional experience and outcomes. Aust N Z J Obstet Gynaecol 2017;57:636–42.
[9] 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;50:458–63.
[10] Pellegrino M, Visconti D, Catania VD, D'Oria L, Manzoni C, Grella MG, et al. Prenatal detection of megacystis: not always an adverse prognostic factor. Experience in 25 consecutive cases in a tertiary referral center, with complete neonatal outcome and follow-up. J Pediatr Urol. 2017;13: 486 e1-e10.
[11] Tschannen R, Gobet R, Wisser J. Prenatal megacystis—is prediction of outcome and renal function possible? Ultraschall Med. 2017(November (21)).
[12] Girard N, Viaris de Lesegno B, Bussiere P, Egoroff C, Cordier AG, Benachi A. Prognosis of isolated first-trimester fetal megacystis with spontaneous resolution. Fetal Diagn Ther 2017;42:271–7.
[13] 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.
[14] Muller Brochut AC, Thomann D, Kluwe W, Di Naro E, Kuhn A, Raio L, et al. Fetal megacystis: experience of a single tertiary center in Switzerland over 20 years. Fetal Diagn Ther 2014;36:215–22.
[15] Bornes M, Spaggiari E, Schmitz T, Dreux S, Czerkiewicz I, Delezoide AL, et al. Outcome and etiologies of fetal megacystis according to the gestational age at diagnosis. Prenat Diag 2013;33:1162–6.
[16] Al-Hazmi H, Dreux S, Delezoide AL, Dommergues M, Lortat-Jacob S, Oury JF, et al. Outcome of prenatally detected bilateral higher urinary tract obstruction or megacystis: sex-related study on a series of 709 cases. Prenat Diag 2012;32:649–54.
[17] 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.
[18] 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.
[19] Van Mieghem T, Ryan G. The PLUTO trial: a missed opportunity. Lancet 2013;382:1471–3.
[20] Taghavi K, Sharpe C, Stringer MD. Fetal megacystis: a systematic review. J Pediatr Urol 2017;13:7–15.
[21] 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.
[22] Sarhan O, Zaccaria I, Macher MA, Muller F, Vuillard E, Delezoide AL, et al. Long-term outcome of prenatally detected posterior urethral valves: single center study of 65 cases managed by primary valve ablation. J Urol 2008;179:307–12 discussion 12-3.
[23] Nassr AA, Shazly SAM, Abdelmagied AM, Araujo Junior 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.
[24] 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.
[25] Morris RK, Malin GL, Khan KS, Kilby MD. Systematic review of the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction. BJOG 2010;117:382–90.
[26] Clark TJ, Martin WL, Divakaran TG, Whittle MJ, Kilby MD, Khan KS. Prenatal bladder drainage in the management of fetal lower urinary tract obstruction: a systematic review and meta-analysis. Obstet Gynecol 2003;102:367–82.