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Outcome of fetal ovarian cysts diagnosed on prenatal ultrasound examination: systematic review and meta-analysis

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KEYWORDS: fetal ovarian torsion; outcome; ovarian cysts; ultrasound

ABSTRACT

Objective *To explore the outcome of fetuses with a prenatal diagnosis of ovarian cyst.*

Methods *The electronic databases MEDLINE and EMBASE were searched using keywords and word variants for 'ovarian cysts', 'ultrasound' and 'outcome'. The following outcomes in fetuses with a prenatal diagnosis of ovarian cyst were explored: resolution of the cyst, change of ultrasound pattern of the cyst, occurrence of ovarian torsion and intracystic hemorrhage, need for postnatal surgery, need for oophorectomy, accuracy of prenatal ultrasound examination in correctly identifying ovarian cyst, type of ovarian cyst at histopathological analysis and intrauterine treatment. Meta-analyses using individual data random-effects logistic regression and meta-analyses of proportions were performed. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale.*

Results *Thirty-four studies (954 fetuses) were included. In 53.8% (95% CI, 46.0–61.5%) of cases for which resolution of the cyst was evaluated (784 fetuses), the cyst regressed either during pregnancy or after birth. The likelihood of resolution was significantly lower in complex* vs *simple cysts (odds ratio (OR), 0.15 (95% CI, 0.10–0.23)) and in cysts measuring* ≥ 40 *mm* vs < 40 *mm (OR, 0.03 (95% CI, 0.01–0.06)). Change in ultrasound pattern of the cyst was associated with an increased risk of ovarian loss (surgical removal or autoamputation) (pooled proportion, 57.7% (95% CI, 42.9–71.8%)). The risk of ovarian torsion was significantly higher for cysts measuring* ≥ 40 *mm compared with* < 40 *mm (OR, 30.8 (95% CI, 8.6–110.0)). The likelihood of having postnatal surgery was higher in patients with cysts* ≥ 40 *mm compared with* < 40 *mm (OR, 64.4 (95% CI, 23.6–175.0)) and in complex compared with simple cysts, irrespective of cyst size (OR, 14.6 (95% CI, 8.5–24.8)). In cases undergoing prenatal aspiration of the cyst, rate of recurrence was 37.9% (95% CI, 14.8–64.3%), ovarian torsion and intracystic hemorrhage were diagnosed after birth in 10.8% (95% CI, 4.4–19.7%) and 12.8% (95% CI, 3.8–26.0%), respectively, and 21.8% (95% CI, 0.9–40.0%) had surgery after birth.*

Conclusion *Size and ultrasound appearance are the major determinants of perinatal outcome in fetuses with ovarian cysts.* *Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Ovarian cysts are the most common abdominal anomalies diagnosed in female fetuses, with an estimated incidence of about 1 in 2600 pregnancies[1]. Although the pathophysiology of ovarian cysts has not yet been elucidated fully, they are usually a benign functional anomaly resulting from excessive stimulation of the fetal ovaries by placental and maternal hormones. They are common in pregnancies complicated by maternal diabetes, pre-eclampsia or rhesus isoimmunization. They are diagnosed most often during the third trimester, especially after 28 weeks' gestation[1,2]. Ovarian cysts are categorized according to their sonographic appearance

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into the following two groups: (1) simple cysts, which are usually anechoic, round, unilocular and thin walled, measuring > 2 cm, and (2) complex cysts, which are usually thick walled and heterogeneous, containing hyperechoic components, free-floating material or intracystic septations, and are commonly considered the result of ovarian torsion or intracystic hemorrhage[3].

Optimal management of fetal ovarian cysts is unclear and the evolution of this anomaly is variable. Although the majority regress either during pregnancy or after birth, torsion and hemorrhage can occur antenatally, thus increasing the risk of surgical intervention and ovarian loss after birth. Prenatal aspiration of the cyst is performed occasionally, especially in the case of large lesions, in order to prevent intrauterine torsion, which may lead to ovarian autoamputation or the need for oophorectomy. However, whether this improves neonatal outcome in these fetuses is yet to be established. Furthermore, the accuracy of antenatal ultrasound examination in correctly identifying fetal ovarian cysts is unknown. Gastrointestinal, renal and genital anomalies are commonly misdiagnosed as ovarian cysts[2]. It is yet to be ascertained whether the ultrasound appearance of the cyst can predict the postnatal outcome or be used to guide prenatal management in these cases.

The aim of this systematic review was to explore the outcome of fetuses with prenatally diagnosed ovarian cysts and to quantify the accuracy of antenatal ultrasound examination in correctly identifying these anomalies.

SUBJECTS AND METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori* protocol recommended for systematic reviews and meta-analyses[4]. The electronic databases MEDLINE and EMBASE were searched on 11 February 2016 utilizing combinations of relevant medical subject heading terms, keywords and word variants for 'ovarian cysts', 'ultrasound' and 'outcome' (Table S1). The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand-searched for additional reports. PRISMA guidelines were followed[5]. The study was registered with the PROSPERO database (registration no. CRD42016035594).

Study selection, data collection and data items

Two authors (F.B. and L.Mar.) independently reviewed all abstracts. Agreement regarding their potential relevance was reached by consensus; full-text copies of eligible papers were obtained and the same two authors independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the two authors and a consensus reached or discussed with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted. Only full-text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than three cases of suspected ovarian cyst, irrespective of whether or not the anomaly was isolated, were also excluded in order to avoid publication bias.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS). According to the NOS, each study is judged on three broad perspectives: selection of the study groups, comparability of the groups and ascertainment of the outcome of interest[6]. Assessment of the selection of a study includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest, and length and adequacy of follow-up[6]. According to the NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars can be given for Comparability.

The incidence of the following outcomes was analyzed in fetuses with a prenatal diagnosis of an ovarian cyst: resolution of the cyst *in utero* or after birth; change of ultrasound pattern from simple to complex cyst; occurrence of ovarian torsion and intracystic hemorrhage; need for postnatal surgery; ovarian loss due to oophorectomy or salpingo-oophorectomy; false-positive rate of prenatal ultrasound diagnosis; histopathological type of ovarian cyst; and intrauterine treatment. Cases undergoing prenatal intervention (cyst aspiration) were evaluated separately in terms of: resolution of the cyst, recurrence of the cyst, increase in cyst size after aspiration, change of ultrasound pattern after intervention, evidence of torsion or hemorrhage after intervention or at birth, need for surgery and preterm delivery or miscarriage due to the invasive procedure.

All of these outcomes were assessed in the overall population of fetuses with a prenatal diagnosis of an ovarian cyst. Furthermore, a subanalysis according to the appearance (simple *vs* complex) and size (< 40 mm *vs* ≥ 40 mm) of the cyst was carried out. Cyst size of 40 mm was used as the cut-off as this has been commonly reported in the literature to represent the highest centile of cyst size.

For ascertainment of data on resolution and change in ultrasound appearance of the cyst, the anomalies were categorized according to their first ultrasound appearance and size, and the prevalence and risks of torsion, hemorrhage, surgery and need for oophorectomy were

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ascertained from the postnatal ultrasound examination or, if not available, the last scan in pregnancy.

Cases that underwent cyst aspiration *in utero* were analyzed separately and were not included in the main analyses. Preterm delivery or miscarriage was considered to be caused by fetal therapy if it occurred within 15 days of the intervention.

Only studies reporting a prenatal diagnosis of ovarian cyst were considered suitable for inclusion in the current systematic review. Postnatal studies or studies from which cases diagnosed prenatally could not be extracted were excluded. Pediatric and surgical series including only symptomatic cases or patients undergoing surgical treatment were also excluded. Studies published before the year 2000 were not included, as we considered that the advances in prenatal imaging techniques and the improvements in diagnosis and definition of fetal anomalies made these studies less relevant. Finally, studies not providing clear classification of the anomaly were not considered suitable for inclusion in the current review.

Statistical analysis

The strength of association between ultrasound characteristics of the cyst and each observed outcome was explored. For quantification of the incidence of these outcomes, meta-analyses of proportions using a random-effects model were used to combine data. Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were carried out with an exploratory aim (data not shown). Tests for funnel-plot asymmetry were not used when the total number of publications included for each outcome was less than 10. In this case, the power of the test is too low to distinguish chance from real asymmetry[7–10]. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance[10].

Furthermore, we evaluated separately the association between ovarian cyst type (complex or simple) and size (≥ 40 mm or < 40 mm) and six clinical outcomes (change of ultrasound pattern (simple cysts becoming complex), cyst resolution, torsion, hemorrhage, postnatal surgery, ovarian loss or oophorectomy). We stratified the meta-analyses, exploring combinations of cyst type and size, thus performing a total of eight direct comparisons for each of the outcomes (excluding change of ultrasound pattern): (1) complex *vs* simple cysts, (2) all cysts ≥ 40 mm *vs* < 40 mm, (3) simple cysts ≥ 40 mm *vs* < 40 mm, (4) complex cysts ≥ 40 mm *vs* < 40 mm, (5) complex cysts ≥ 40 mm *vs* simple cysts ≥ 40 mm, (6) complex cysts < 40 mm *vs* simple cysts ≥ 40 mm, (7) complex cysts ≥ 40 mm *vs* simple cysts < 40 mm and (8) complex cysts < 40 mm *vs* simple cysts < 40 mm.

We included observational cohort studies in which: (1) many comparisons reported zero events in one group, (2) several comparisons reported zero events in both groups and (3) exposed and unexposed group sizes were frequently severely unbalanced. In such cases, many of the most commonly used meta-analytical methods, including those using risk difference (which could be used to handle total zero-event studies), can produce biased estimates when events are rare[11,12]. When many studies are also substantially unbalanced, the best performing methods are the Mantel–Haenszel odds ratio (OR) without zero-cell continuity corrections, logistic regression and an exact method[13,14]. Mantel–Haenszel ORs cannot be computed in studies reporting zero events in both groups, the exclusion of which may, however, cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect[11]. Therefore, to keep all studies in the analyses, we performed all meta-analyses using individual data random-effects logistic regression, with single study as the cluster unit. The pooled datasets with individual data were reconstructed using published 2×2 tables. When one of the overall pooled arms showed no event, we used exact logistic regression.

As a likely consequence of non-randomization, dissimilarity of the populations and lack of fixed criteria for when to treat, several of the comparisons showed an extreme imbalance in the success rate between the groups being compared (e.g. 44/67 *vs* 0/69). In addition to the computational issues, in such cases the ORs may be of limited interest and sensitivity, and specificity may be more informative. We thus computed the overall sensitivity and specificity (and related 95% CI) for each comparison according to the efficient-score method (corrected for continuity) described by Newcombe[14].

All analyses were performed using Stata version 13.1 (2013; Stata Corp., College Station, TX, USA).

RESULTS

Study selection and characteristics

A total of 1483 articles were identified, of which 52 were assessed for eligibility for study inclusion (Table S2). Thirty-four studies including a total of 954 fetuses with a prenatal diagnosis of ovarian cysts were included in the systematic review (Table 1 and Figure 1)[15–48].

Quality assessment of the included studies was performed using the NOS for cohort studies (Table 2). Most of the included studies showed an overall good quality with regard to selection and comparability of the study groups and ascertainment of the outcomes of interest. The main weaknesses of the studies were their retrospective design, small sample size and lack of detailed ultrasound characteristics of the cysts in some of the included studies.

Synthesis of results

Resolution of the cyst

Twenty-nine studies including 784 fetuses with a prenatal diagnosis of ovarian cyst evaluated resolution of the cyst.

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Table 1 Characteristics of studies on fetuses with prenatally diagnosed ovarian cysts included in systematic review

Study	*Country*	*Study design*	*Imaging technique*		*Fetuses* (n)	*GA at diagnosis (weeks)**	*Cyst diameter (mm)**	*Age at surgery**	*Age at follow-up**
			Prenatal	*Postnatal*					
Catania (2016)[15]	Italy	Retro	US	US, MRI	25	33 (22 to 39)	NS	NS	5 y
Thakkar (2015)[16]	UK	Retro	US	US	34	NS	NS	NS	NS
Nakamura (2015)[17]	Japan	Retro	US	US	33	32 (22 to 37)	47 (17–79)	NS	NS
Marchitelli (2015)[18]	France	Retro	US	US, MRI	17	NS	NS	NS	NS
Açıkgöz (2015)[19]	Turkey	Retro	US	US, MRI	17	30 ± 6.4	39.8 ± 13.4	NS	NS
Jwa (2015)[20]	Japan	Retro	US, MRI	US	21	33.9 (29.9 to 36.9)	37 (15–52)	1 day to 4 mo	NS
Papic (2014)[21]	UK	Retro	US	US	25	NS	55.1 (24–150)	12 (3–64) wk	NS
Karakuş (2014)[22]	Turkey	Retro	US	US	37	33.1 ± 3.2	41.5 (10–60)	NS	3 mo
Turgal (2013)[23]	Turkey	Retro	US	US	29	28.4 (23 to 37)	40.9 (11–90)	2–4 mo	2–9 mo
Amari (2013)[24]	Germany	Retro	US	NS	35	32 + 0 (14 + 6 to 39 + 2)	NS	NS	NS
Dimitraki (2012)[25]	Greece	Retro	US	US	16	32.4 (30 to 37)	37.7 (21–74)	1 mo	3–12 mo
Gaspari (2012)[26]	France	Retro	US	US	5	> 32	52.4 (40–60)	1–3 mo	4.14 (1.5–6.7) y
Lecarpentier (2012)[27]	France	Retro	US	NS	26	NS	NS	NS	NS
Nemec (2012)[28]	Austria	Retro	US, MRI	US	16	31 + 2 (23 + 0 to 35 + 5)	NS	NS	NS
Noia (2012)[29]	Italy	Retro	US	US	13	32 (27 to 36)	46 (31–74)	NS	2 mo to 3 y
Aqrabawi (2011)[30]	Jordan	Retro	US	US	12	NS	30–100	NS	1 mo to 6 y
Akin (2010)[31]	Turkey	Retro	US	US	18	34 (32 to 38)	53.0 (25–80)	1–23 days	NS
Eleftheriades (2010)[32]	Greece	Retro	US	US	7	32 (31 + 1 to 32 + 4)	37 (27–61)	NS	NS
Ben-Ami (2010)[33]	Israel	Retro	US	US	21	33 (28 to 37)	42.4 (10–60)	44.2 (1–115) days	6.6 (1.3–11.6) y
Zampieri (2008)[34]	Italy	Retro	US	US, MRI	57	34 (32 to 37)	50.0 (27–75)	NS	1–5 y
Godinho (2008)[35]	Portugal	Retro	US	US	5	31 + 6 (29 to 35)	38.3 (29–60)	10–11 days	NS
Shimada (2008)[36]	Japan	Retro	US	US	16	Third trimester	46.6 (23–75)	Within 10 mo	2 mo
Monnery-Noché (2008)[37]	France	Retro	US	US	65	33 (24 to 39)	43.5 (17–130)	3 (0–119) days	3 mo (11 days to 6 y)
Galinier (2008)[38]	France	Retro	US	US	79	32 (26 to 39)	43.5 (20–90)	NS	11 mo (6 mo to 10 y)
Kwak (2006)[39]	South Korea	Retro	US	US	17	34 (30 to 38)	49 (33–78)	1 day to 3 wk	1–24 mo
Foley (2005)[40]	Australia	Retro	US	US	11	Second to third trimester	39.6 (7–70)	7–8 mo	12.9 mo (3 mo to 6 y)
Enríquez (2005)[41]	Spain	Retro	US, MRI	US, MRI	18	33 to 37	24–112	NS	3–15 mo
Comparetto (2005)[42]	Italy	Retro	US	US	32	34 (32 to 37)	27–75	NS	1–5 y
Quarello (2003)[43]	France	Retro	US	US	12	31	NS	NS	NS
Mittermayer (2003)[44]	Germany	Retro	US	US	61	32 (24 to 38)	42 ± 12	2 h to 6 wk	7 days to 12 mo
Heling (2002)[45]	Germany	Retro	US	US	64	35 (26 to 40)	32 (17.5–55.0)	1–14 days	NS
Bagolan (2002)[46]	Italy	Prosp	US	US	80	33.6 (23 to 39)	39 (23–85)	NS	NS
Perrotin (2000)[47]	France	Retro	US	US	3	31 (29 to 32)	31 (16–44)	No surgery	2–4 wk
Luzzatto (2000)[48]	Italy	Retro	US	US	27	33 (28 to 36)	43.3 (24–77)	0–17 mo	3 mo to 9 y

Only first author of each study is given. *Median (range), range, mean or mean ± SD. GA, gestational age; mo, months; MRI, magnetic resonance imaging; NS, not stated; Prosp, prospective; Retro, retrospective; US, ultrasound; wk, weeks; y, years.

About half of all cysts resolved during pregnancy or after birth (pooled proportion (PP), 53.8% (95% CI, 46.0–61.5%)) (Figure 2a). Resolution of the cyst occurred in 69.4% (95% CI, 59.0–79.0%) of simple cysts and in 84.8% (95% CI, 70.0–95.2%) of cysts measuring < 40 mm. The proportions of cases with resolution of the cyst according to size and ultrasound appearance are reported in Table S3. Complex cysts (OR, 0.15 (95% CI, 0.10–0.23)) and cysts measuring ≥ 40 mm (OR, 0.03 (95% CI, 0.01–0.06)) were less likely to regress than simple cysts or cysts measuring < 40 mm, respectively (Table 3).

Change of ultrasound pattern, ovarian torsion and intracystic hemorrhage

More than 20% (PP, 23.6% (95% CI, 14.4–34.4%)) of all simple cysts demonstrated a change in ultrasound pattern to that of a complex cyst during pregnancy or at birth (Figure 2b). The risk of change in ultrasound pattern during pregnancy was significantly higher in cysts ≥ 40 mm compared with those < 40 mm (OR, 3.16 (95% CI, 1.02–9.7); I^2, 0%). In those cases, the occurrence of ovarian loss, either due to surgical removal or ovarian autoamputation, was high (PP, 57.7% (95% CI, 42.9–71.8%); I^2, 7.1%).

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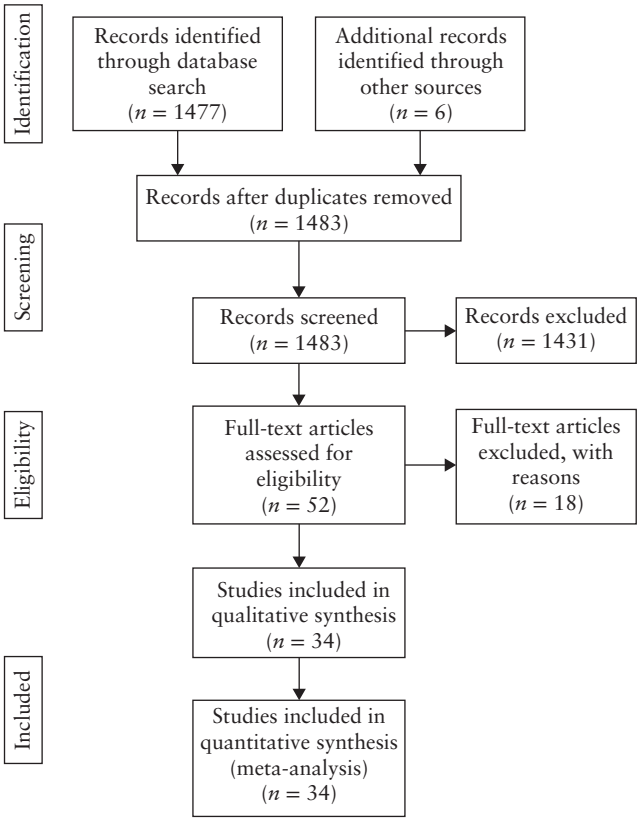

Figure 1 Flowchart of inclusion of studies in systematic review.

The overall incidence of ovarian torsion of the cyst was 21.8% (95% CI, 15.2–29.2%) (Figure 2c). The corresponding values for torsion in simple and complex cysts were 6.0% (95% CI, 3.6–8.9%) and 44.9% (95% CI, 31.7–58.4%), respectively (Table S4). The risk of ovarian torsion was significantly higher in cysts ≥ 40 mm compared with those < 40 mm, irrespective of their ultrasound appearance (OR, 30.8 (95% CI, 8.6–110.0)) (Table 4). Furthermore, risk of torsion was significantly higher for complex cysts than for simple cysts (OR, 59.1 (95% CI, 24.7–141.0)).

Intracystic hemorrhage occurred in 6.8% (95% CI, 3.7–10.8%) of cases (Figure 2d, Table S5). The risk of hemorrhage was significantly higher for complex *vs* simple cysts (OR, 28.6 (95% CI, 4.9–∞)), for cysts ≥ 40 mm *vs* < 40 mm (OR, 31.7 (95% CI, 3.7–270.0)) and for simple cysts ≥ 40 mm *vs* < 40 mm (OR, 63.4 (95% CI, 10.7–∞)) (Table 5).

Surgery

Thirty studies including 761 fetuses with a prenatal diagnosis of ovarian cyst explored the incidence of postnatal surgery. Overall, 39.5% (95% CI, 30.1–49.3%) of fetuses with a prenatal diagnosis of ovarian cysts confirmed at birth had surgical intervention (Figure 2e). The corresponding values in fetuses with simple and complex ovarian cysts were 24.6% (95% CI, 14.2–36.9%) and 64.8% (95% CI, 52.2–76.3%), respectively (Table S6).

Table 2 Quality assessment of studies in systematic review according to Newcastle–Ottawa Scale

Author	*Selection*	*Outcome*	*Comparability*
Catania (2016)[15]	★★	★★	★
Thakkar (2015)[16]	★★★	★★	★★
Nakamura (2015)[17]	★★	★	★
Marchitelli (2015)[18]	★★	★	★
Açıkgöz (2015)[19]	★★	★★	★
Jwa (2015)[20]	★★	★★	★
Papic (2014)[21]	★★	★★	★
Karakuş (2014)[22]	★★	★★	★
Turgal (2013)[23]	★★	★	★
Amari (2013)[24]	★	★	★
Dimitraki (2012)[25]	★★	★	★
Gaspari (2012)[26]	★★	★★	★
Lecarpentier (2012)[27]	★★	★★	★
Nemec (2012)[28]	★★	★★	★
Noia (2012)[29]	★★	★	★
Aqrabawi (2011)[30]	★★	★★	★
Akin (2010)[31]	★★	★★	★
Eleftheriades (2010)[32]	★★	★★	★
Ben-Ami (2010)[33]	★★	★★	★
Zampieri (2008)[34]	★★	★★	★
Godinho (2008)[35]	★★	★★	★
Shimada (2008)[36]	★★	★	★
Monnery-Noché (2008)[37]	★★	★★	★
Galinier (2008)[38]	★★	★★	★
Kwak (2006)[39]	★★	★★	★
Foley (2005)[40]	★★	★★	★
Enríquez (2005)[41]	★★	★★	★
Comparetto (2005)[42]	★★	★★	★
Quarello (2003)[43]	★★	★★	★
Mittermayer (2003)[44]	★★	★★★	★★
Heling (2002)[45]	★★	★	★
Bagolan (2002)[46]	★★	★★	★★
Perrotin (2000)[47]	★★	★★	★
Luzzatto (2000)[48]	★★	★★	★★

Only first author of each study is given. A study can be awarded a maximum of one star for each numbered item within Selection and Outcome categories and a maximum of two stars for Comparability.

The likelihood of having surgery was higher in patients with cysts ≥ 40 mm compared with < 40 mm (OR, 64.4 (95% CI, 23.6–175.0)) and in complex cysts compared with simple cysts, irrespective of the cyst size (OR, 14.6 (95% CI, 8.5–24.8)) (Table 6).

Ovarian loss, due to oophorectomy or salpingo-oophorectomy, occurred in 25.1% (95% CI, 17.2–34.0%) of cases that underwent surgery (Figure 2f, Table S7). Both complex cysts (OR, 35.1 (95% CI, 17.0–72.7)) and cysts ≥ 40 mm (OR, 58.9 (95% CI, 19.2–181.0)) were significantly associated with an increased risk of ovarian loss (Table 7).

Intrauterine treatment

Twelve studies including 56 fetuses that underwent intrauterine aspiration of the cyst were included in the systematic review. After aspiration of the cyst, the incidence of recurrence was 37.9% (95% CI, 14.8–64.3%),

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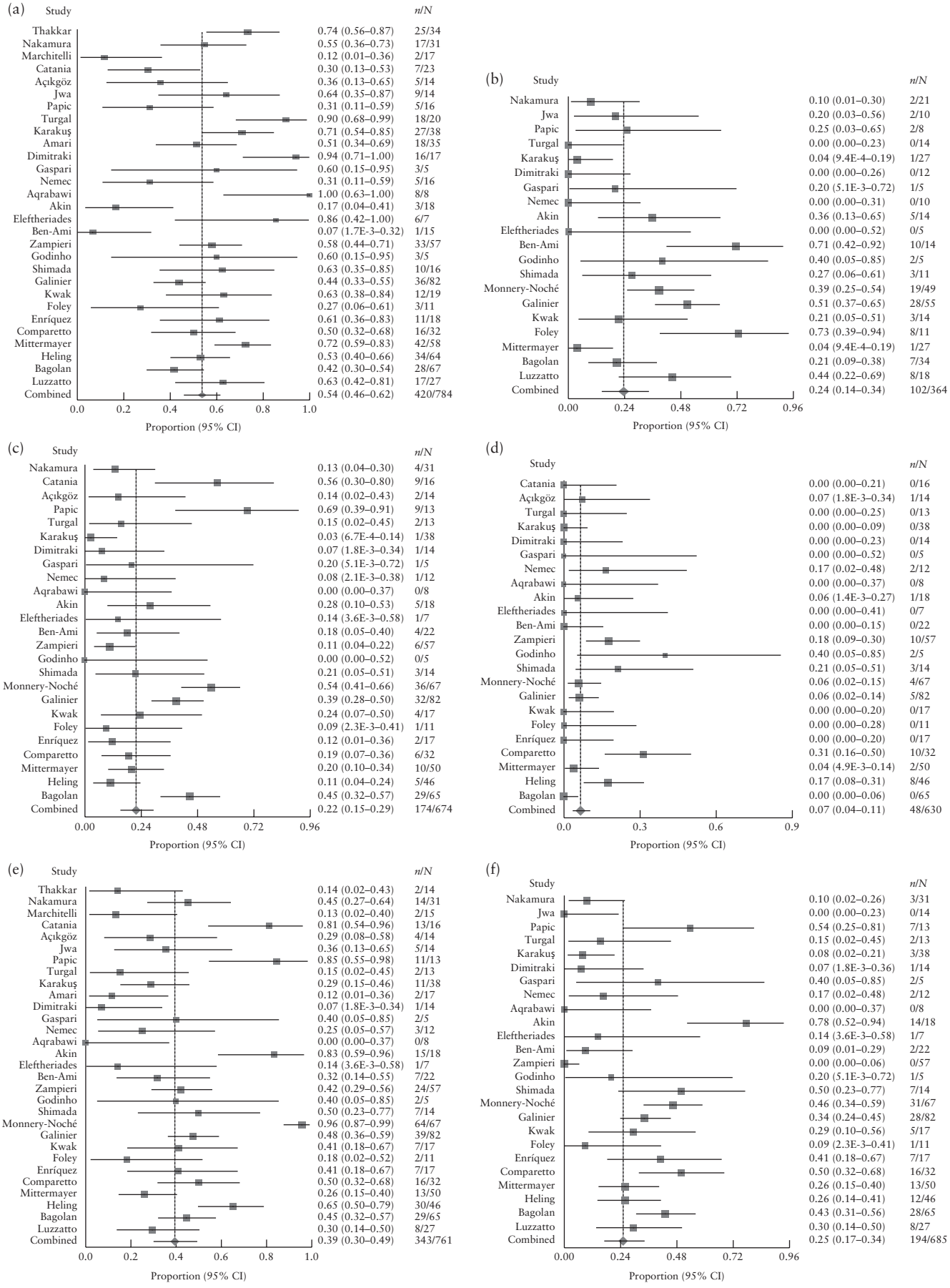

Figure 2 Pooled proportions for: (a) resolution of cyst; (b) change of ultrasound pattern in cyst from simple to complex; (c) ovarian torsion; (d) intracystic hemorrhage; (e) postnatal surgery; and (f) ovarian loss, in fetuses with ovarian cysts. *n*/*N*, numbers of cysts.

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Table 3 Pooled odds ratios (ORs) for likelihood of resolution of fetal ovarian cyst, according to cyst size and/or ultrasound appearance

Variable	*Studies* (n)	*Fetuses* (n/N vs n/N)	*Pooled OR*	P	*Sensitivity** (%)	*Specificity** (%)
Complex *vs* simple cysts	20	68/224 *vs* 231/341	0.15 (0.10–0.23)	< 0.001	58.6 (52.5–64.6)	77.3 (72.0–81.8)
Cysts ≥ 40 mm *vs* cysts < 40 mm	16	60/192 *vs* 149/168	0.03 (0.01–0.06)	< 0.001	87.4 (80.8–92.1)	71.3 (64.6–77.2)
Simple cysts ≥ 40 mm *vs* < 40 mm	16	45/134 *vs* 140/156	0.02 (0.00–0.06)	< 0.001	84.8 (76.1–90.8)	75.7 (68.7–81.5)
Complex cysts ≥ 40 mm *vs* < 40 mm	9	17/54 *vs* 25/28	0.06 (0.01–0.21)	< 0.001	92.5 (78.5–98.0)	59.5 (43.3–74.0)
Complex cysts ≥ 40 mm *vs* simple cysts ≥ 40 mm	11	19/60 *vs* 42/83	0.40 (0.18–0.88)	0.022	50.0 (38.8–61.2)	68.9 (55.6–79.8)
Complex cysts < 40 mm *vs* simple cysts ≥ 40 mm	11	26/30 *vs* 39/73	4.93 (1.36–17.8)	0.015	10.5 (3.0–25.7)	60.0 (47.1–71.7)
Complex cysts ≥ 40 mm *vs* simple cysts < 40 mm	12	20/62 *vs* 71/83	0.04 (0.01–0.12)	< 0.001	77.8 (64.1–87.5)	78.0 (67.9–85.7)
Complex cysts < 40 mm *vs* simple cysts < 40 mm	11	26/30 *vs* 64/74	0.56 (0.09–3.38)	0.5	25.6 (9.6–58.0)	71.1 (60.5–79.9)

Values in parentheses are 95% CI. *Computed for reverse outcome 'no resolution'.

Table 4 Pooled odds ratios (ORs) for likelihood of ovarian torsion in fetuses with ovarian cyst, according to cyst size and/or ultrasound appearance

Variable	*Studies* (n)	*Fetuses* (n/N vs n/N)	*Pooled OR*	P	*Sensitivity* (%)	*Specificity* (%)
Complex *vs* simple cysts	19	139/253 *vs* 7/242	59.1 (24.7–141.0)	< 0.001	95.2 (90.0–97.9)	67.3 (62.1–72.2)
Cysts ≥ 40 mm *vs* cysts < 40 mm	13	45/116 *vs* 3/121	30.8 (8.6–110.0)	< 0.001	93.8 (81.8–98.4)	62.4 (55.1–69.3)
Simple cysts ≥ 40 mm *vs* < 40 mm	12	14/82 *vs* 1/123	26.7 (3.3–214.0)	0.002	93.3 (66.0–99.7)	64.2 (56.9–70.9)
Complex cysts ≥ 40 mm *vs* < 40 mm	9	37/61 *vs* 3/33	16.2 (4.3–61.6)	< 0.001	92.5 (78.5–98.0)	55.6 (41.5–68.8)
Complex cysts ≥ 40 mm *vs* simple cysts ≥ 40 mm	9	37/61 *vs* 1/40	82.0 (9.1–743.0)	< 0.001	97.4 (84.6–99.9)	61.9 (48.8–73.6)
Complex cysts < 40 mm *vs* simple cysts ≥ 40 mm	9	3/35 *vs* 2/38	1.8 (0.2–13.7)	0.6	60.0 (17.0–92.7)	52.9 (45.0–65.0)
Complex cysts ≥ 40 mm *vs* simple cysts < 40 mm	11	38/66 *vs* 0/62	114.0 (19.3–∞)*	< 0.001	100 (88.6–100)	68.9 (58.1–78.0)
Complex cysts < 40 mm *vs* simple cysts < 40 mm	10	3/39 *vs* 0/60	6.2 (0.6–∞)*	0.11	100 (31.0–100)	62.5 (52.0–72.0)

Values in parentheses are 95% CI. *Exact logistic regression as no logistic regression model was possible due to zero events in reference group. ∞, infinity.

whereas an increase in cyst size occurred in 6.9% (95% CI, 2.0–14.5%) of cases. Almost half of the cysts aspirated *in utero* did not recur, either during pregnancy or after birth (PP, 48.9% (95% CI, 25.0–74.0%)). Change of ultrasound pattern in the cyst after aspiration, from a simple to complex appearance, occurred in 7.9% (95% CI, 2.6–15.8%) of cases, whereas ovarian torsion and intracystic hemorrhage were diagnosed after birth in 10.8% (95% CI, 4.4–19.7%) and 12.8% (95% CI, 3.8–26.0%) of the treated cases, respectively. The rate of preterm delivery or miscarriage due to the invasive procedure was 5.1% (95% CI, 0.7–13.0%; 1/44; I^2, 0%) and 21.8% (95% CI, 0.9–40.0%) had surgery after birth (Table 8 and Figure 3).

False-positive rate of prenatal diagnosis and histopathological assessment

The false-positive rate of prenatal ultrasound examination detecting fetal ovarian cysts was 7.5% (95% CI, 4.4–11.4%). Of these cases with misdiagnosis of ovarian cyst, almost half were gastrointestinal anomalies (PP, 54.1% (95% CI, 28.1–78.9%)). Furthermore, urogenital and renal anomalies were diagnosed incorrectly as ovarian cysts in 14.9% (95% CI, 6.6–25.6%) and 10.3% (95% CI, 4.0–19.1%) of cases, respectively (Table S8).

Histopathological assessment of the ovarian cyst following surgery was available for 385 cases. The majority of cysts were either follicular or theca lutein (93.0% (95% CI, 87.7–96.8%)), and cystadenoma and

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Table 5 Pooled odds ratios (ORs) for risk of intracystic hemorrhage in fetuses with ovarian cyst, according to cyst size and/or ultrasound appearance

Variable	*Studies* (n)	*Fetuses* (n/N vs n/N)	*Pooled OR*	P	*Sensitivity* (%)	*Specificity* (%)
Complex *vs* simple cysts	17	19/210 *vs* 0/205	28.6 (4.9–∞)*	< 0.001	100 (79.1–100)	51.8 (46.7–56.8)
Cysts ≥ 40 mm *vs* cysts < 40 mm	12	2/15 *vs* 0/35	31.7 (3.7–270.0)	0.002	100 (82.0–100)	72.9 (57.9–84.3)
Simple cysts ≥ 40 mm *vs* < 40 mm	10	20/70 *vs* 0/115	63.4 (10.7–∞)*	< 0.001	100 (80.0–100)	69.7 (62.0–76.5)
Complex cysts ≥ 40 mm *vs* < 40 mm	7	5/44 *vs* 1/26	2.8 (0.3–28.5)	0.4	83.3 (36.5–99.1)	39.1 (27.4–52.1)
Complex cysts ≥ 40 mm *vs* simple cysts ≥ 40 mm	7	5/44 *vs* 0/28	4.6 (0.6–∞)*	0.16	100 (46.3–100)	41.8 (30.1–54.5)
Complex cysts < 40 mm *vs* simple cysts ≥ 40 mm	7	1/28 *vs* 0/26	0.9 (0.0–∞)*	0.9	100 (5.5–100)	49.1 (35.3–63.0)
Complex cysts ≥ 40 mm *vs* simple cysts < 40 mm	9	7/49 *vs* 0/54	11.9 (1.7–∞)*	0.009	100 (56.1–100)	56.3 (45.8–66.2)
Complex cysts < 40 mm *vs* simple cysts < 40 mm	8	1/32 *vs* 0/52	1.6 (0.0–∞)*	0.8	100 (5.5–100)	62.7 (51.3–72.8)

Values in parentheses are 95% CI. *Exact logistic regression as no logistic regression model was possible due to zero events in reference group. ∞, infinity.

Table 6 Pooled odds ratios (ORs) for likelihood of postnatal surgery in fetuses with ovarian cyst, according to cyst size and/or ultrasound appearance

Variable	*Studies* (n)	*Fetuses* (n/N vs n/N)	*Pooled OR*	P	*Sensitivity* (%)	*Specificity* (%)
Complex *vs* simple cysts	22	197/290 *vs* 77/292	14.6 (8.5–24.8)	< 0.001	71.9 (66.1–77.1)	69.8 (64.3–74.8)
Cysts ≥ 40 mm *vs* cysts < 40 mm	15	96/138 *vs* 9/140	64.4 (23.6–175.0)	< 0.001	91.4 (83.9–95.8)	75.7 (68.5–81.8)
Simple cysts ≥ 40 mm *vs* < 40 mm	14	67/90 *vs* 1/133	3998 (233–68 626)	< 0.001	98.5 (91.0–99.9)	85.2 (78.4–90.2)
Complex cysts ≥ 40 mm *vs* < 40 mm	11	56/75 *vs* 7/42	48.8 (10.4–229.0)	< 0.001	88.9 (77.8–95.0)	64.8 (50.6–77.0)
Complex cysts ≥ 40 mm *vs* simple cysts ≥ 40 mm	11	58/75 *vs* 23/48	17.7 (4.4–71.3)	< 0.001	71.6 (60.3–80.8)	59.5 (43.3–74.0)
Complex cysts < 40 mm *vs* simple cysts ≥ 40 mm	11	7/44 *vs* 23/46	0.2 (0.1–0.8)	0.016	23.3 (10.6–42.7)	38.3 (26.4–51.8)
Complex cysts ≥ 40 mm *vs* simple cysts < 40 mm	13	61/80 *vs* 1/72	2015 (71.0–57 179)	< 0.001	98.4 (90.2–99.9)	78.9 (68.8–86.5)
Complex cysts < 40 mm *vs* simple cysts < 40 mm	12	7/48 *vs* 1/70	45.3 (1.2–1722)	0.040	87.5 (46.7–99.3)	80.5 (74.3–85.5)

Values in parentheses are 95% CI.

teratoma were diagnosed in 2.1% (95% CI, 0.9–3.7%) and 1.5% (95% CI, 0.5–2.9%) of cases, respectively (Table S9).

DISCUSSION

Main findings

The findings from this systematic review showed that a large proportion of fetal ovarian cysts regress either during pregnancy or after birth. Simple cysts may change in ultrasound appearance during pregnancy and become complex, which is associated with an increased risk of ovarian loss. The size and appearance of the cyst are the major determinants of perinatal outcome and are associated with an increased risk of ovarian torsion, intracystic hemorrhage and need for oophorectomy. The false-positive rate of prenatal ultrasound examination in the detection of fetal ovarian cysts is low, although it is not uncommon for gastrointestinal, renal and urogenital anomalies to be misdiagnosed as ovarian cysts. The very small number of included cases precluded extrapolation of robust evidence on the value of intrauterine treatment of ovarian cysts.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, different periods of follow-up, dissimilarity of the populations (due to various inclusion criteria) and lack of fixed criteria for when to treat and postnatal confirmation represent the

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Table 7 Pooled odds ratio (OR) for likelihood of ovarian loss at surgery (due to oophorectomy or salpingo-oophorectomy) in fetuses with ovarian cyst, according to cyst size and/or ultrasound appearance

Variable	*Studies* (n)	*Fetuses* (n/N vs n/N)	*Pooled OR*	P	*Sensitivity* (%)	*Specificity* (%)
Complex *vs* simple cysts	20	139/263 *vs* 17/276	35.1 (17.0–72.7)	< 0.001	89.9 (82.9–93.3)	67.6 (62.4–72.2)
Cysts ≥ 40 mm *vs* cysts < 40 mm	15	76/138 *vs* 5/140	58.9 (19.2–181.0)	< 0.001	93.8 (85.6–97.8)	68.5 (61.5–74.8)
Simple cysts ≥ 40 mm *vs* < 40 mm	13	26/84 *vs* 0/129	80.3 (13.8–∞)*	< 0.001	100 (84.0–100)	69.0 (61.8–75.4)
Complex cysts ≥ 40 mm *vs* < 40 mm	10	42/62 *vs* 4/38	21.8 (5.8–81.9)	< 0.001	91.3 (78.3–97.2)	63.0 (48.7–75.4)
Complex cysts ≥ 40 mm *vs* simple cysts ≥ 40 mm	10	42/62 *vs* 10/62	35.0 (5.93–206.0)	< 0.001	80.8 (67.0–89.9)	72.2 (60.2–81.8)
Complex cysts < 40 mm *vs* simple cysts ≥ 40 mm	10	4/40 *vs* 10/40	1.6 (0.2–13.8)	0.7	28.6 (9.6–58.0)	45.5 (33.3–58.1)
Complex cysts ≥ 40 mm *vs* simple cysts < 40 mm	12	44/67 *vs* 0/68	∞ (500.0–∞)*	< 0.001	100 (89.9–100)	74.7 (64.3–83.0)
Complex cysts < 40 mm *vs* simple cysts < 40 mm	11	4/44 *vs* 0/66	8.4 (1.0–∞)*	0.047	100 (39.6–100)	62.3 (52.3–71.3)

Values in parentheses are 95% CI. *Exact logistic regression as no logistic regression model was possible due to zero events in reference group. ∞, infinity.

Table 8 Pooled proportions (PPs) for different outcomes in fetuses with ovarian cyst treated prenatally

Outcome	*Studies* (n)	*Fetuses* (n/N)	*Raw proportion (%)*	I^2 *(%)*	*PP (%)*
Recurrence of cyst	12	19/56	33.93 (21.8–47.8)	74	37.88 (14.8–64.3)
Resolution of cyst	12	31/56	55.36 (41.5–68.7)	70	48.86 (25.0–73.0)
Increase of cyst size	12	2/56	3.57 (0.4–12.3)	0	6.90 (2.0–14.5)
Change of ultrasound pattern of cyst from simple to complex	12	2/56	3.57 (1.0–12.1)	0	7.90 (2.6–15.8)
Ovarian torsion	12	4/56	7.14 (2.0–17.0)	0	10.83 (4.4–19.7)
Intracystic hemorrhage	12	5/56	8.93 (3.0–19.6)	35.3	12.78 (3.8–26.0)
Surgery	12	9/56	16.07 (7.6–28.3)	40.5	21.81 (0.9–38.0)
Preterm birth or miscarriage	6	1/44	2.27 (0.1–12.0)	0	5.10 (0.7–13.0)

Values in parentheses are 95% CI.

major limitations of this systematic review. Assessment of the potential publication bias was also problematic because of the nature of the outcome evaluated (outcome rates, with the lefthand side limited to a value of zero), which limits the reliability of funnel plots, and because of the small number of individual studies, which strongly limits the reliability of formal tests.

Most of the observed outcomes were reported in only a limited proportion of the included studies. Furthermore, we could not stratify the analysis according to different cut-offs for cyst size in view of the fact that the majority of these were reported in only a few studies, thus considerably limiting the interpretation of the results. The ascertainment of some of the outcomes observed, such as surgery or need for oophorectomy, was also considerably biased by the different postnatal management strategies adopted in different centers. Large lesions usually undergo surgical intervention, irrespective of the presence of symptoms, in order to reduce the risk of complications, such as torsion and hemorrhage, which may lead to ovarian loss. In this scenario, the results from this systematic review may have overestimated some of the adverse outcomes associated with ovarian cysts.

The assessment of the role of intrauterine therapy was also problematic. Ovarian cysts usually regress during pregnancy and, thus, the role of *in-utero* cyst aspiration in preventing the occurrence of torsion or hemorrhage could not be quantified completely. Furthermore, the very small number of included cases, different gestational ages at intervention, timepoints at postnatal follow-up and lack of ascertainment according to cyst size and appearance did not allow us to draw any conclusion on the role of prenatal cyst aspiration in the management of ovarian cysts. Therefore, an adequately powered randomized control trial is needed in order to ascertain the value of prenatal cyst aspiration.

Despite these limitations, the present review represents the best published estimate of the investigated outcomes in fetuses diagnosed with ovarian cysts.

Implications for clinical practice

Prenatal and postnatal management of fetal ovarian cysts is challenging. The evidence is sparse and is derived mainly from postnatal series reporting high rates of complications and need for surgical intervention. The findings from this systematic review showed that ultrasound appearance and

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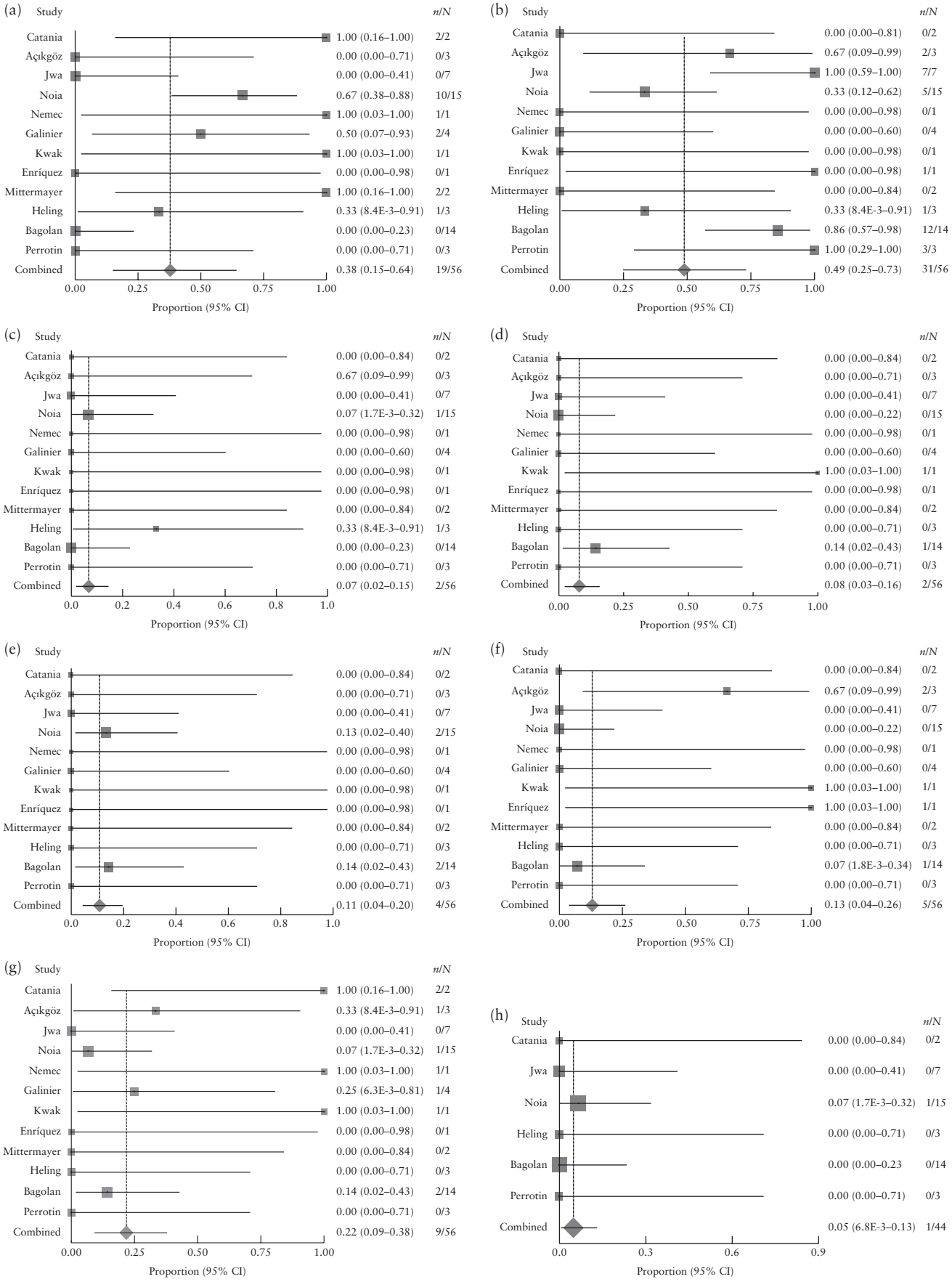

Figure 3 Pooled proportions for perinatal outcomes of: (a) recurrence of cyst; (b) resolution of cyst; (c) increase in cyst size; (d) change of ultrasound pattern in cyst; (e) ovarian torsion; (f) intracystic hemorrhage; (g) surgery; and (h) preterm birth or miscarriage, in fetuses with ovarian cyst treated by intrauterine aspiration.

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cyst size are the major determinants of perinatal outcome in these cases and can be used to tailor the optimal postnatal management of affected patients.

Simple cysts may occasionally change their ultrasound appearance and become complex, either during pregnancy or after birth, and this was associated with a significantly increased risk of ovarian loss due to surgical oophorectomy or ovarian autoamputation. Ultrasound surveillance of the fetus should be scheduled in order to look for early signs of complications of the cyst, such as an increase in size or appearance of intracystic echoes. However, the optimal perinatal management of these cases is controversial[49,50]. Iatrogenic preterm delivery and prompt surgical intervention may further compromise these patients on the basis that ovarian function might have already been compromised. In this scenario, especially in cases remote from term, ultrasound monitoring of the cyst seems the most reasonable and safe option.

Complex cysts have been reported to be strongly associated with ovarian torsion requiring oophorectomy[1,2]. In the present review, the likelihood of surgical removal of the ovary was higher in large and complex cysts. Despite this, not all complex cysts showed signs of torsion, thus questioning whether postnatal intervention should be arranged immediately after birth in newborns with complex lesions.

The role of intrauterine aspiration of the ovarian cyst is controversial[51]. The findings from this systematic review suggest that almost half of the ovarian cysts aspirated *in utero* regress during pregnancy or after birth. Furthermore, the risks of torsion, hemorrhage and need for postnatal surgical intervention are relatively small. However, these findings come from retrospective series including mainly highly selected cases. The very small number of included studies, different timepoints at fetal intervention and follow-up and variation in cyst size and appearance did not allow us to draw any robust conclusion. Aspiration of the cyst *in utero* might be considered, especially in the case of large cysts presenting before term, in order not to compromise the reproductive capacity of the fetus in adult life or in case of the cyst causing compression on adjacent structures, leading to bowel obstruction or impaired flow in the ductus venosus. However, a randomized and adequately powered control trial is needed in order to ascertain the role, if any, of intrauterine aspiration of the cyst in the prenatal management of ovarian cysts.

Ovarian cysts are one of the most common abdominal cystic anomalies diagnosed prenatally. The present review showed that a small proportion of renal, gastrointestinal and genital anomalies can be misdiagnosed as ovarian cysts. Almost 15% of complex urogenital anomalies, such as persistence of urogenital sinus or cloaca, were misdiagnosed as ovarian cysts. Because these anomalies are associated with worse postnatal and surgical outcomes compared with ovarian cysts, a thorough ultrasound examination should be arranged in order to not misdiagnose them as ovarian cysts.

In conclusion, a large proportion of fetal ovarian cysts diagnosed prenatally regress during pregnancy or after birth. The risk of torsion is particularly high in the case of large cysts. The change of ultrasound pattern of the cyst during pregnancy is associated with a high risk of ovarian loss. The size and appearance of the cyst are the major determinants of perinatal outcome and are associated with an increased risk of ovarian torsion, intracystic hemorrhage and need for oophorectomy. Future randomized trials are needed in order to ascertain the role of fetal therapy in the management of these cases.

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Search strategy using MEDLINE and EMBASE

Table S2 Excluded studies and reason for exclusion

Table S3 Pooled proportions of rate of resolution of fetal ovarian cysts either during pregnancy or after birth

Table S4 Pooled proportions of occurrence of ovarian torsion in fetuses with a prenatal diagnosis of ovarian cyst

Table S5 Pooled proportions of occurrence of intracystic hemorrhage in fetuses with prenatal diagnosis of ovarian cyst

Table S6 Pooled proportions of rate of postnatal surgery in fetuses with prenatal diagnosis of ovarian cyst

Table S7 Pooled proportions of rate of ovarian loss at surgery (due to oophorectomy or salpingo-oophorectomy) in fetuses with prenatal diagnosis of ovarian cyst

Table S8 Pooled proportions of rate of false-positive diagnoses of ovarian cyst according to cyst type

Table S9 Pooled proportions of different histopathological diagnoses of fetal ovarian cysts

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