



A retrospective multicenter study of the natural history of fetal ovarian cysts

Athanasios Tyraskis^a, Spyros Bakalis^b, Carolina Scala^c, Argyro Syngelaki^d, Stefano Giuliani^e, Mark Davenport^a, Anna L. David^b, Kypros Nicolaides^d, Simon Eaton^f, Paolo De Coppi^{f,*}

^a Paediatric Surgery Unit, King's College Hospital, London, UK

^b Institute for Women's Health, University College London, UK

^c Fetal Medicine Unit, St. George's Hospital, London, UK

^d Harris Birthright Centre, King's College Hospital, London, UK

^e Department of Paediatric and Neonatal Surgery, St. George's University Hospitals NHS Foundation Trust, Blackshaw Rd, SW17 0QT, London, UK

^f Stem Cells and Regenerative Medicine, DBC, UCL Institute of Child Health and Great Ormond Street Hospital London, UK

ARTICLE INFO

Article history:

Received 21 September 2017

Received in revised form 31 January 2018

Accepted 4 February 2018

Key words:

Fetal ovarian cyst

Ovarian torsion

Prenatal diagnosis

Ultrasound

Prenatal aspiration

Fetal intervention

ABSTRACT

Aim: We investigated the natural history of fetal ovarian cysts to estimate the risk of torsion according to size. **Methods:** Cases were identified from 1/1/2000 until 1/1/2015. Data were collected pre- and postnatally on cyst size and sonographic features until an outcome of surgery, torsion, or resolution. Fisher's exact test for categorical data and logistic regression for continuous data were used to test the significance of size on torsion; P value <0.05 was considered significant.

Results: 37 patients with unilateral ovarian cysts were included. 12 (32%) resolved spontaneously prenatally, 14 (38%) resolved spontaneously postnatally, 5 (14%) underwent surgery postnatally and 6 (16%) cases underwent torsion. Rate of torsion increased with size from 0% (n = 0) in cysts ≤20 mm to 33% (n = 2) in cysts >50 mm; however, the overall trend failed to reach statistical significance (P = 0.1). Cysts of 0–40 mm had a significantly higher rate of spontaneous resolution (90% vs. 44% in >40 mm, P = 0.003), but the rate of torsion was not significantly different (10% in 0–40 mm vs. 25% in >40 mm, P = 0.26). The median time to postnatal resolution was 10 (5–27) weeks in those treated conservatively.

Conclusion: Cysts >40 mm are significantly less likely to resolve spontaneously; however torsion showed no significant correlation with cyst size. No complications were observed in cysts <20 mm.

Level of Evidence: IV, case series with no comparison group.

© 2018 Published by Elsevier Inc.

Follicular ovarian cysts in fetal life are a response to maternal and placental estrogens and gonadotrophins and occur as commonly as 1 in every 1000 fetuses [1]. These cysts are often treated conservatively prenatally and managed expectantly postnatally until resolution. There are increasing data to suggest that there is a significant risk of ovarian torsion prenatally and that this risk is related to the cyst diameter [2]. This has led some groups to attempt prenatal aspiration of cysts to decrease their size and hopefully their chance of prenatal torsion. Most groups advocate a cutoff cyst diameter of 40 or 50 mm as an indication for prenatal aspiration [3–5]. However, all previous studies have investigated a single cyst size cutoff to determine the risk of torsion rather than describe the prevalence of torsion according to cyst size.

The sonographic appearance of the cyst may also be significant in determining treatment strategy in addition to its size. Simple cysts are

assumed to be viable whereas complex cysts (especially if a fluid-debris level is present internally) have a high likelihood of already having torqued. Thus the simple cysts would be the target of treatment in order to prevent ovarian loss [6,7].

Owing to the rarity of large ovarian cysts and incomplete follow-up, the natural evolution of these cysts has not been well studied, and the degree of risk of torsion with increasing cyst diameter has yet to be quantified.

The aim of this study was to investigate the natural history of prenatally diagnosed ovarian cysts; to estimate the risk of torsion for cysts according to their size and sonographic appearance, and to assess likelihood of cyst resolution.

1. Method

This is a multicenter retrospective study of pregnant women referred to three tertiary-referral fetal medicine units with follow-up of their infants in three pediatric surgery centers. Three fetal medicine

* Corresponding author at: Developmental Biology & Cancer Programme, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

E-mail address: p.decoppi@ucl.ac.uk (P. De Coppi).

centers and their respective pediatric surgical centers were included in this study (King's College Hospital, St. George's Hospital, University College London Hospital) with a further contribution from the department of pediatric surgery at Great Ormond Street Hospital (the referral center for babies born at University College London Hospital). Cases of fetal ovarian cysts were identified using the ViewPoint (GE Healthcare, UK) ultrasound (US) database at each hospital. To ensure complete capture of fetal ovarian cysts, a search for "ovarian or pelvic or abdominal cyst(s)" was performed on scans from January 2000 until January 2015. All identified cases were screened for eligibility where inclusion criteria were unilateral or bilateral cyst(s) that were suspected to be of ovarian origin. Patients were excluded if they were not followed up in one of the three fetal medicine centers, but rather had just been referred for a second opinion and one ultrasound scan to ensure completeness of both prenatal and postnatal information.

Data on cyst dimensions and sonographic appearance were gathered from all prenatal scans from time of diagnosis until birth. Postnatal follow up data were obtained from all patients until the time of resolution, aspiration or surgical excision. Any cases which during follow-up were determined to have cysts of nonovarian origin were excluded. The size measurements used to subdivide patients for the subsequent analysis were the maximum diameter of the cyst at the time of the first prenatal US scan in one of the three included tertiary fetal medicine centers. Median and interquartile range of cyst size according to gestational age was reported and a subgroup analysis was performed according to the maximum diameter on any prenatal US rather diagnosis. Patients who underwent prenatal aspiration were included in the overall analysis and more information on their individual clinical course was provided.

Ovarian loss in patients with ovarian cysts may occur owing to torsion, and for the purpose of this study was defined as: a necrotic ovary at the time of surgery, or a complex cyst which regressed without any identifiable ovarian tissue on the ipsilateral side on more than one

US scans post regression. Simple cysts were defined as a thin-walled cyst with anechoic contents, and complex cysts included those with internal septations, debris, or other echoic content which did not appear solid (solid complex cysts were excluded owing to the risk of being teratomas). Postnatal resolution was defined as resorption of the cyst with two identifiable ovaries on US. Prenatal resolution was defined as resorption of the cyst on subsequent antenatal US (most of these patients did not go on to have postnatal US).

This study was registered as an audit approved by the Clinical Audit and Safety Department of Great Ormond Street Hospital (approval number: 1524) and therefore did not require formal ethical committee approval.

Two-tailed Fisher's exact tests were used to test for significant differences between the different size groups; GraphPad Prism (Version 6)® was used for this statistical analysis. 95% level of confidence was defined as significant. Continuous data were reported as median and interquartile range. Overall trend according to size was tested using a logistic regression on STATA 13®. Finally a 95% confidence interval of proportion was calculated using the GraphPad Quick Calcs online software. A P value of <0.05 was considered significant.

2. Results

A total of 109 patients were identified with a diagnosis of fetal ovarian cyst(s). 58/109 were referred to our centers only for a second opinion, and had no further contact besides a single consultation. As we did not have a complete data for follow-up and outcomes they were excluded from our study. 14 were lost to follow-up either pre or postnatally, and the remaining 37 patients were included in the study (Fig. 1). Spontaneously resolution occurred in 12/37 (32%) cysts prior to birth, and 14 (38%) resolved spontaneously after birth. Postnatal surgery occurred in 7 infants and 4 of those were found to have torsed necrotic ovaries and in 1 infant the ovary was twisted along the axis of

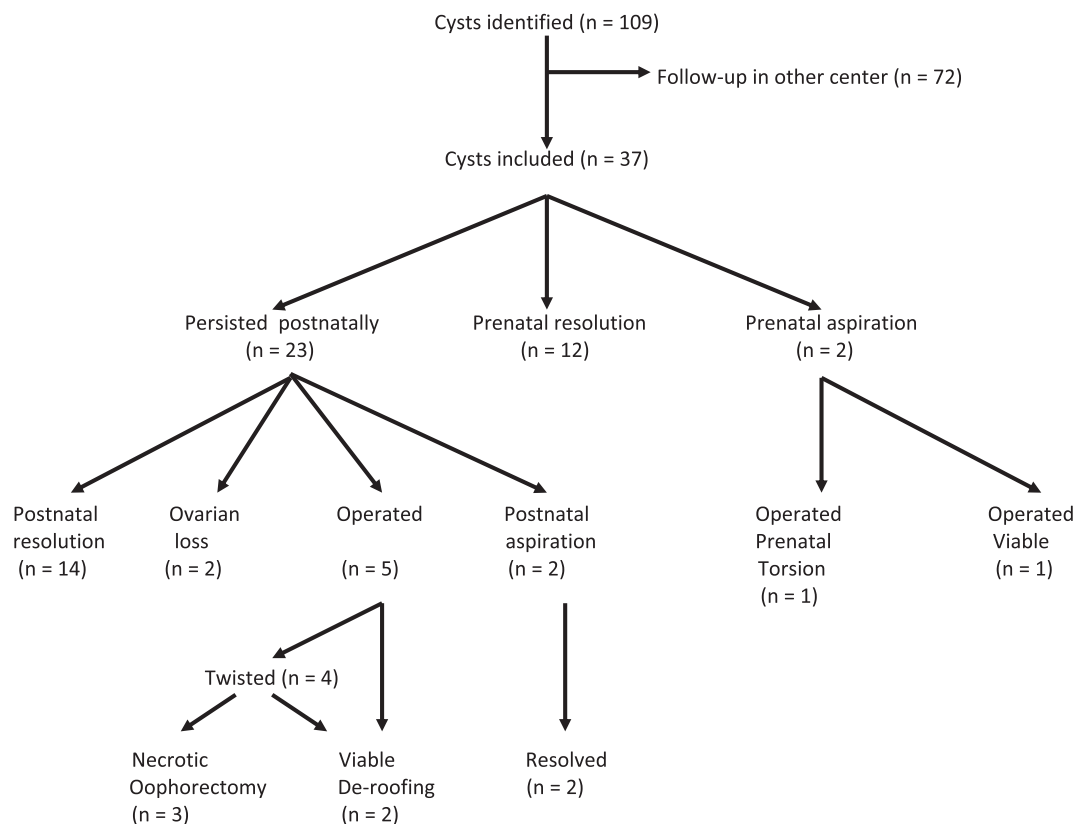


Fig. 1. Flowchart of outcomes for all patients.

Table 1

Table showing the outcomes of fetal ovarian cyst cases according to the cyst maximum diameter at prenatal diagnosis.

Maximum diameter at diagnosis (mm)	Number of cysts	Resolution prenatally	Resolution postnatally	Aspiration (performed prenatally)	Postnatal surgery	Torsion
0–20	7	6	1	0	0	0
21–30	7	3	3	0	1	1
31–40	7	3	3	0	1	1
41–50	10	0	5	2 (0)	2	2
>50	6	0	2	2 (2)	3	2
Total	37	12	14	4 (2)	7	6

the Fallopian tube but was viable following detorsion and de-roofing. There were 6 cases of ovarian loss in total; 4 of those were identified at the time of postnatal surgery and the remaining 2 had a complex cyst which regressed without any remaining ovarian tissue on the ipsilateral side on multiple sonographic examinations (ovarian loss in Fig. 1).

The distribution according to size and frequency of outcomes can be seen in Table 1. Rates of torsion increased incrementally from 0% for cysts 0–20 mm, 14% ($n = 1$) in cysts 21–30 mm, and 31–40 mm, 20% ($n = 2$) in cysts 41–50, and up to 33% ($n = 2$) in cysts >50 mm at the time of diagnosis. Prenatal resolution occurred less often with increasing size: 86% ($n = 6$) of cysts 0–20 mm, 43% ($n = 3$) of those 21–40 mm, and 0% of those >40 mm. Of the cysts which remained postnatally, a similar decrease in spontaneous resolutions was observed: 75% ($n = 7$) of those 0–40 mm, 50% ($n = 5$) of those 41–50 mm, and 33% ($n = 2$) of those >50 mm. No cyst <20 mm underwent any invasive procedure, compared to 14% ($n = 2$) of cysts 21–40 mm, 40% ($n = 4$) of patients in the 41–50 mm, and 50% ($n = 3$) of patients with cysts >50 mm at diagnosis. Interestingly, a significant difference is present when performing a subgroup analysis comparing cysts of up to 40 mm to those that were >40 mm. Smaller cysts of ≤ 40 mm resolved spontaneously in 90% ($n = 19$) of cases compared to only 44% ($n = 7$) of cysts >40 mm ($P = 0.003$). However, there was no significant difference in the rate of torsion of cysts ≤ 40 mm, 10% ($n = 2$), compared to 25% ($n = 4$) in cysts >40 mm ($P = 0.26$). Of those cysts that resolved postnatally without intervention, the median number of weeks to resolution was 10 with an interquartile range of 5–27 weeks.

Of relevance, diameters also changed during the gestation with the median value for the largest diameter of the cyst increasing from 19th to the 34th week of gestation after which we found that it plateaued (Fig. 2). At the time of diagnosis, 25 (68%) of the cysts were simple in sonographic appearance, 9 (24%) were complex, and for 3 (8%) the appearance was not commented on. Of the 25 that were simple, 18 (72%) resolved without any intervention, 8 prenatally and 10 postnatally. A total of 7 (28%) of the 25 simple cysts had an invasive procedure, 2 (8%) had a postnatal aspiration (and both subsequently resolved), and 5 (20%) patients underwent operations (1 of which had already undergone a prenatal aspiration), 2 (8%) had viable ovaries and 2 (8%) had torted necrotic ovaries. Of those 2 that were necrotic, both had a complex appearance on the first postnatal ultrasound scan which was

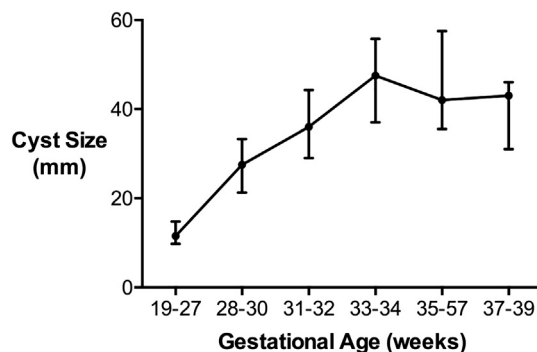


Fig. 2. The median and interquartile range values for maximum diameter according to the gestational age of the patient when the US was performed.

done in the first week of life, and one of which had an autoamputated cyst which was ‘wandering’ and was located in the right upper quadrant of the abdomen on one scan.

Table 2 outlines the outcomes according to the ultrasonographic appearance. Nine cysts were complex at the time of diagnosis, 3 (33%) underwent torsion, and 6 (67%) in total resolved (4 prenatally and 2 postnatally). All four that resolved prenatally were <40 mm at the time of diagnosis. One of the complex cysts which underwent torsion was 28 mm at the time of diagnosis; the other two were 54 mm and 97 mm. Three patients did not have the appearance of their cyst commented on at the time of diagnosis. Two of those resolved postnatally and one had a repeat ultrasound a week later prenatally and the cyst was found to be complex. Postnatally this patient had a laparoscopic resection of a necrotic ovarian cyst that had undergone torsion.

Two prenatal aspirations were performed on the basis of their size. One cyst was simple, initially measuring 64 mm but growing to 102 mm prenatally, occupying most of the fetal abdomen. 320 ml of straw colored fluid was aspirated prenatally; however, this patient subsequently required surgical deroofting owing to reaccumulation of fluid postnatally, at which time the ovary was seen to be viable. The second was a large complex cyst measuring 97 mm at diagnosis and the decision was made to aspirate owing to signs of fetal anemia at which time blood stained fluid was aspirated. The first postnatal ultrasound and operation were performed in the first week of life and found the cyst to be in the epigastric region. Subsequently this patient became symptomatic and a decision was made to operate, and was found to have a necrotic ovary separate to the Fallopian tube of which only a remnant remained (presumably following resorption of necrotic tissue), suggesting that the torsion had occurred prenatally.

Postnatal aspiration was employed on two cysts, one measuring 45 mm at diagnosis and one measuring 50 mm at diagnosis. Both had grown 5–10 mm after birth leading to the decision to aspirate. They had good outcomes and these cysts went on to resolve completely within the first year of life.

3. Discussion

There is a paucity of actual evidence for the predictability of torsion of >40 mm or >50 mm ovarian cysts which are often deemed as ‘large’ and at high risk of torsion according to a single size cutoff [3,8]. Our study is the largest case-series to date that describes the natural history of prenatally diagnosed ovarian cysts according to a more detailed size categorization (multiple progressive size groups rather than two groups based on an arbitrary cutoff). We found that cysts of <20 mm in size had no adverse outcomes nor did they require any postnatal intervention. Rates of torsion and surgery both increased with cyst size but a logistic regression using the actual cyst measurements failed to show any significant differences in the rate of torsion as cyst size increased ($p = 0.1$). This may be owing to insufficient number of cases in our study. Spontaneous resolution of the cysts also decreased consistently with increasing cyst size. Although there was no clear cutoff for a size at which the risks of torsion or incidence of surgery increased dramatically, our data indicated an increment in all outcomes (need for surgery, torsion or failure to resolve spontaneously) for cysts of 40 mm and greater. For this reason we did a subgroup analysis comparing ovarian cysts

Table 2
Table of outcomes according to initial appearance of cyst on ultrasound.

Cyst appearance on ultrasound	Number of cysts	Resolution prenatally	Resolution postnatally	Aspiration (performed prenatally)	Postnatal surgery	Torsion
Simple	25	8	10	3 (1)	5	2
Complex	9	4	2	1 (1)	2	3
Unknown	3	0	2	0	0	1

measuring up to 40 mm to those >40 mm; the rates of spontaneous resolution of the larger cysts were significant lower (44% vs. 90%, $P < 0.01$).

The timing of torsion in our cohort is not obvious but the clinical evidence points more to prenatal torsion. Of the 6 cases of torsion in our study, 1 had an operation in the first week of life that only found a cyst which was separate from a remnant of the fallopian tube indicating that the torsion had undergone a significant period of time prior, only consistent with prenatal torsion. Of the remaining 5 patients, 3 of those had operations after the first week of life and the remaining 2 had a cyst which resolved after the neonatal period with no ovary identifiable on repeated ultrasound scans, thus, making it impossible to be certain regarding the timing of torsion. As none of these patients became symptomatic postnatally, and 5 (83%) were complex on US prenatally with the last 1 having a complex appearance on the first postnatal US in the first week of life, there is a strong suspicion that torsion occurred prenatally. This finding could make an argument for prenatal aspiration [2], a technique still rarely performed and utilized by us only in 2 cases.

Authors have supported the use of prenatal aspiration as a method of decreasing the risk of torsion in larger cysts owing to the assumed greater risk of torsion in those cysts. The size at which aspiration is considered is 40–50 mm depending on the study [2,3]. Encouraging results from one study using prenatal aspiration show significantly decreased risk of torsion from 85% rate of torsion in cysts 50 mm or larger which were not aspirated to 14% in those which were [3]. Our study did not confirm that cysts larger than 50 mm had such high rates of torsion; nevertheless, larger prospective studies are necessary for more accurate quantification of this risk, and the subsequent potential benefit of prenatal aspiration.

Postnatal aspiration was effective in both patients in which it was performed; however there is a paucity of cases in the literature in order to corroborate its effectiveness. The infrequent reporting of postnatal aspiration rather than surgery in the literature makes evaluating its outcomes particularly difficult. It is dependent on the particular expertise being available and favorable positioning of the cyst with no overlying bowel to make safe aspiration possible. Some authors have employed it in 1–2 cases in their larger cohorts of which one complication of intraperitoneal bleed has been noted [10]. Another caution which other authors have emphasized is the reaccumulation of the cysts, with one study observing this in 1 of 5 cases aspirated [6,8], a complication not occurring when surgical deroofting or cystectomy is performed [9].

Being complex in appearance is not a predictive risk factor for torsion but rather an indicator that there has been a hemorrhagic process into the cyst. The cause can be benign such as a ruptured blood vessel, or may represent a necrotic process leading to vessel disruption and bleeding into the cyst. All of our cases that underwent torsion and necrosis were found to have a complex sonographic appearance prior to the diagnosis of necrosis. One third of our cases that were

complex had undergone torsion, slightly lower than one of the largest studies in the literature; Galinier et al. found that of 55 hemorrhagic cysts 30 (55%) were either absent or unidentifiable on follow-up indicating ovarian loss [6].

4. Conclusion

Cysts in our study tended to increase in size until the 34th week of gestation. While this retrospective study confirmed that size is a significant factor in the clinical evolution of fetal ovarian cysts, we showed that cysts greater than 40 mm, rather than 50 mm as previously reported, are significantly less likely to resolve spontaneously. Larger studies are needed to investigate if cysts greater than 40 mm are at significantly higher risk of torsion. Cysts less than 20 mm in size are unlikely to have any complications. Aspiration both pre and postnatally may provide a therapeutic option but clinicians must be aware of risks of reaccumulation of fluid as well as that a complex sonographic appearance could be secondary to both hemorrhage into an otherwise viable ovarian cyst or torsion and necrosis, and may represent worse candidates for a therapeutic aspiration.

Acknowledgments

ALD is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. PDC is supported by NIHR and the Great Ormond Street Hospital Biomedical Research Centre and SE is supported by Great Ormond Street Hospital Biomedical Research Centre and by Great Ormond Street Hospital Children's Charity.

References

- [1] Pilar SF, Juan D, Martinez C, et al. Quiste de ovario fetal: diagnostico prenatal, evolucion perinatal y tratamiento. *Ginecol Obstet Mex* 2012;80:84–90.
- [2] Giorlandino C, et al. Successful intrauterine therapy of a large fetal ovarian cyst. *Prenat Diagn* 1990;10:473–5.
- [3] Bagolan P, et al. The management of fetal ovarian cysts. *J Pediatr Surg* 2002;37:25–30.
- [4] Noia G, et al. Invasive fetal therapies: approach and results in treating fetal ovarian cysts. *J Matern Fetal Neonatal Med* 2012;25:299–303.
- [5] Crombleholme TM, Craig SD, Garmel S, et al. Fetal ovarian cyst decompression to prevent torsion. *J Pediatr Surg* 1997;32:1447–9.
- [6] Galinier P, et al. Fetal ovarian cysts management and ovarian prognosis: a report of 82 cases. *J Pediatr Surg* 2008;43:2004–9.
- [7] Enriquez G, et al. Conservative versus surgical treatment for complex neonatal ovarian cysts: outcomes study. *Am J Roentgenol* 2005;185:501–8.
- [8] Luzzatto C, Midrio P, Toffolutti T, et al. Neonatal ovarian cysts: management and followup. *Pediatr Surg Int* 2000;16:56–9.
- [9] Mizuno M, Kato T, Hebiguchi T, et al. Surgical indications for neonatal ovarian cysts. *Tohoku J Exp Med* 1998;186:27–32.
- [10] Monnery-Noche M-E, et al. Fetal and nonatal ovarian cysts: is surgery indicated? *Prenat Diagn* 2008;28:15–20.