A systematic review and meta-analysis on fetal ovarian cysts: impact of size, appearance and prenatal aspiration.

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What's already known about this topic?

Fetal ovarian cysts have long been associated with a risk of torsion pre- and post-natally; cyst size is a known risk factor for torsion. Until now there has been no estimate of the risk of torsion according to ovarian cyst size. Prenatal ultrasound guided cyst aspiration is used rarely and its efficacy is still debated. The scarcity of cases increases the challenge to design studies and answer the pertinent clinical questions.

What does this study add?

In this systematic review and meta-analysis we quantified the risk of torsion according to ovarian cyst size. Furthermore, we were able to perform comparison of simple cysts ≥40mm to identify the potential benefit of prenatal aspiration over conservative management. Finally, we estimated the proportion of cases that tortured pre-natally and again relate this to the size at diagnosis.

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Abstract

Objective

To compare outcomes of ultrasound-guided aspiration of fetal ovarian cysts with conservative management.

Method

A systematic review of MEDLINE and Web of Science included studies reporting outcomes (pre- and post-natal torsion, spontaneous resolution, and surgery) of fetuses with ovarian cysts. Subgroup analysis was performed according to cyst diameter at diagnosis and cysts ≥ 40mm.

Results

92 non-randomized studies reported on 380 cysts (324 observed, 56 aspirated in-utero) in 365 fetuses. All studies were case reports or series with high heterogeneity and risk of bias. The overall spontaneous resolution rate of conservatively managed cysts was 46%, yet decreased with increasing cyst size. Risk of prenatal ovarian torsion in conservatively managed cases depended on cyst size and was particularly important in the range 30-59mm (15-34%). The rate of prenatal torsion in simple cysts ≥40mm was lower in aspirated than conservatively managed cysts (0% versus 10%, p=0.03). Aspirated cysts had lower rates of postnatal surgery (7%) compared to conservatively managed cysts (49%, p<0.001).

Conclusion

30–59mm cysts were at highest risk of torsion. Simple cysts >40mm had lower rates of torsion when aspirated prenatally. Randomized studies and safety data are needed prior to routine prenatal ovarian cyst aspiration.
Introduction

The incidence of fetal ovarian cysts has been estimated to be as high as 1 in every 1,000 fetuses.\(^1\) The suspected mechanism for the formation of ovarian cysts in-utero is a dysregulated response of follicles to high levels of estradiol and gonadotrophins. Ovarian cysts are not considered pathologic unless they are at least 20mm in greatest diameter,\(^2\) and smaller cysts of at least 1mm in size are common. In one study of 332 neonatal deaths and stillbirths ovarian cysts were found to be present in 34% of cases and were increasingly common later in gestation.\(^18\) In case reports, ovarian cysts have been associated with hypothyroidism, diabetic mothers, and pregnancies complicated by rhesus isoimmunisation, but these associations have not been confirmed in larger studies. Ovarian malignancies are exceedingly rare in the prenatal/neonatal period, with only one reported in a large case series, and in a further series of 91 paediatric ovarian tumours, none were found before the age of one year.\(^12\)\(^20\)

For the past three decades fetal ovarian cysts have been increasingly diagnosed through the use of prenatal ultrasound. Despite the rapid increase in the number of cases and cohorts that have been reported in the literature, there remains uncertainty regarding their pre- and post-natal management. Cysts can undergo torsion in utero, resulting in loss of the ovary, fallopian tube, or both, which could compromise future fertility. Very large cysts distend the fetal abdomen and could lead to dystocia in labour. The risk of torsion with fetal ovarian cysts has led groups to perform prenatal ultrasound guided aspiration in larger simple cysts with the aim to reduce the chance of prenatal torsion.\(^3\)\(^4\) A balance is needed however between the potential for complications from ultrasound guided prenatal aspiration including haemorrhage, preterm premature rupture of the membranes (PPROM) and preterm birth, against the risk of prenatal torsion. Indications for performing cyst aspiration vary, with some groups reporting aspirating only simple cysts with a diameter of 40 or 50mm or greater.\(^5\)\(^6\)\(^7\) Prenatal aspiration has been reported to result in lower rates of ovarian torsion compared to conservative management, but few studies have used this method and there still remains significant doubt on its safety and results.\(^5\)
Even the significance of a complex or simple appearance to the cyst has been subject to debate, especially in the management of cysts post-natally. Retrospective cohort studies suggest that ovarian loss is more common in complex cysts.\textsuperscript{5} Ovarian cysts which already have undergone torsion are more likely to be complex in appearance, thus surgery for complex cysts may be less likely to be beneficial. Many practitioners therefore propose that only women whose fetus has a simple ovarian cyst be offered prenatal aspiration.\textsuperscript{68} A complex cyst poses diagnostic uncertainty and some authors suggest that it is an indication for post-natal surgery.\textsuperscript{8}

While a consensus exists in the adult literature that there is a higher risk of torsion for larger simple and complex ovarian cysts, it remains unclear at which size torsion becomes a significant risk when ovarian cysts are diagnosed \textit{in utero} or in infants.\textsuperscript{87}

\textbf{Objectives}

We performed a systematic review and meta-analysis of pregnant women whose fetus had a prenatal diagnosis of an ovarian cyst to investigate how the outcomes of cyst resolution, post-natal surgery, and prenatal torsion after prenatal aspiration compared with conservative management. We also aimed to identify the risk of ovarian torsion according to size and sonographic appearance of ovarian cysts in those cases managed conservatively.

\textbf{Methods}

A Medline\textsuperscript{®} and Web of Science\textsuperscript{™} search of journal articles for: (fetal OR antenatal* OR prenatal* OR neonatal) AND ovarian AND cyst* was performed electronically on December 16\textsuperscript{th}, 2014, for studies published from 1980 to the search date. Titles and abstracts were screened for relevance by two reviewers (AT and SB), relevant references were reviewed in full and disagreements were resolved through
discussion and consensus; references were managed using Endnote™ software. All relevant articles were read in full by AT and SB. The study population was any patient with a prenatally diagnosed ovarian cyst, and outcomes investigated were: cyst resolution, pre or post-natal torsion, or surgery. The studied intervention was prenatal aspiration or conservative management. The inclusion criteria for our meta-analysis was any study which individually and separately stated for each of their study patients data on the greatest diameter of each individual ovarian cyst at time of diagnosis, and followed up with radiological investigations until one of the specified outcomes was reached. The inclusion criteria for the aspirated group also allowed for inclusion of studies that set clear size criteria for performing aspiration if individual sizes were not given (e.g. greater than 40mm), and undertook follow-up with radiological investigations for the same aforementioned outcomes. Both retrospective and prospective studies were included and animal studies were excluded. Eligible studies included were of English, French, Spanish or German language. Furthermore, any study which grouped the cohort of conservatively managed patients together and did not report individual size at diagnosis and outcomes was excluded. The study protocol was modified according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Risk of bias assessment was performed on included studies using the QUADS-2 tool. 

Outcomes which we investigated were: resolution of the cyst with an ovary present, resolution of a cyst with no detectible ovary, prenatal torsion, total torsion, and surgery. Further variables collected were cyst size at the time of diagnosis and sonographic appearance at the time of diagnosis. Data for each eligible study were entered into a central database independently and then subsequently reconfirmed. 

We defined prenatal torsion as either: intrauterine ovarian auto-amputation, “wandering” cyst prenatally with absent ovary at first neonatal scan, or ovarian necrosis confirmed from histological sample taken at time of surgery within the neonatal period in an otherwise asymptomatic neonate. If age at operation was not precisely stated then other evidence was taken into account to determine time of torsion. The total
torsion group included babies who developed symptoms of torsion at any age, and who had surgery with histological confirmation of torsion in or after the neonatal period. Where available we gathered the appearance of the cyst on ultrasound (simple or complex) according to the Nussbaum criteria.  

Absolute risk was reported and proportions were compared using a two tailed Fisher’s exact test on GraphPad Prism 6® software. Data were also meta-analyzed taking into account between-study differences using a random binary effects model in MetaAnalyst 3.1 in order to generate confidence intervals. Sensitivities and specificities were calculated and the Receiver operating characteristic (ROC) curve was plotted on GraphPad Prism 6®.

A subgroup analysis was performed on any ovarian cysts that were 40mm or larger at the time of diagnosis comparing conservatively managed cysts to those treated with prenatal aspiration. Furthermore, this comparison was repeated for a further subgroup of only simple ovarian cysts that were 40mm or larger at diagnosis.

**Results**

**Search Results**

The MEDLINE®, and Web of Science™ search yielded 1,172 articles of which 263 were relevant, with a total of 1,663 patients. Of those articles, 114 were included for a qualitative analysis. Five articles were excluded due to being review articles and 169 articles were excluded as they did not meet our inclusion criteria, leaving 89 articles that met the inclusion criteria for the meta-analysis. All included studies were observational studies, no randomised controlled trial was found. Details on all studies are included in the Supplementary Table. 373 patients were included in our study with a total number of cysts included in the meta-analysis of 380. 7 patients had bilateral ovarian cysts over 20mm. The literature was largely...
heterogeneous. Variability was seen amongst different authors in: indications for surgery, indications for aspiration, interpretations of US findings, and methods of reporting data. Furthermore, 75% of the papers included had 10 patients or less.

Ovarian cyst cases

324 cysts were treated conservatively by observation alone prenatally and 56 cysts underwent ultrasound guided prenatal aspiration. Gestational age at diagnosis was available for 270 fetuses with conservatively managed cysts (median gestational age at diagnosis = 33 weeks, inter-quartile range 31-35 weeks). Gestational age at diagnosis for aspirated cysts was available for 29 of the patients. The median gestational age at diagnosis was 32 weeks, and the inter-quartile range was 30 – 33 weeks.

Table 1 outlines the number of patients in each ovarian cyst size group and the frequency of the following outcomes: cyst resolution without any postnatal surgery, prenatal cyst resolution, total torsion (prenatal and postnatal), prenatal torsion, and postnatal surgery.

Spontaneous cyst resolution

Only 10% of the cysts resolved prenatally in the conservatively managed group, with highest rates in smaller cysts measuring 20-29mm (26%), and lower resolution rates for cysts measuring greater than 40mm (3%-9%). The overall spontaneous resolution rate of conservatively managed ovarian cysts was 46%. Small cysts under 29mm had a high rate of spontaneous resolution when managed conservatively (87%). The rate of spontaneous resolution diminished with increasing cyst size to rates of 17 – 21% for cysts 60mm or larger. Of the 56 cysts prenatally aspirated, 13 (23%) resolved completely during the prenatal period following aspiration, however, of the 324 ovarian cysts conservatively managed, only 34 (10%) resolved spontaneously prenatally (p=0.01). Furthermore, significantly more cysts of the prenatally aspirated group required no post-natal intervention (82% vs. 46% p<0.001), Table 1.
The rate of total torsion (prenatal or postnatal, Figure 1A), and the rate of prenatal torsion (Figure 1B) was evaluated according to prenatal ovarian cyst size. When comparing the rate of torsion in the prenatal aspiration group (11%) to the conservatively managed groups, there was no difference in the rate of torsion for ovarian cysts measuring 20-29mm (10%, p=0.54), 30-39mm (20%, p=0.11) or 80-110mm (18%, p=0.39). However, cysts measuring between 40-79mm did have higher rates of total torsion if managed conservatively when compared to the prenatally aspirated group as follows: 40-49mm group (39%, p<0.001), 50-59mm group (43%, p<0.001), 60-69mm group (35%, p<0.01), and 70-79mm group (45%, p<0.001).

Rates of prenatal torsion are more informative in identifying if prenatal aspiration is effective in preventing ovarian accidents and are displayed in Figure 1B. The overall rate of prenatal torsion in the aspiration group was 4%. This was not significantly different from the rate of prenatal torsion in conservatively managed cysts of the following sizes: 20-29mm (3%, p=0.45), 60-69mm (12%, p=0.14), and 80-110mm (18%, p=0.12). However the prenatal torsion rate was significantly higher in cysts sized 30-39mm (15% p=0.02), 40-49mm (27% p<0.001), 50-59mm (34% p<0.001), and 70-79mm (21% p=0.02).

**Postnatal Surgery**

The aspiration group also had lower rates of surgery postnatally (7%) compared to the conservatively managed cyst group (49%, p<0.001). Larger cysts had higher rates of postnatal surgery compared to the aspirated group ranging from 25% for cysts measuring 30-39mm up to 82% for those measuring 80-110mm (Table 1). Only the 20-29mm cyst size group did not have an increased frequency of postnatal surgery (10%, p=0.70).
Cysts of 40mm and greater

Most groups performing prenatal aspiration used a minimum cyst size of 40-50mm as their cut-off criterion. In order to compare similar ovarian cyst size groups, we compared outcomes in conservatively managed cysts with aspirated cysts that measured greater than or equal to 40mm (Figure 2). For all outcomes, the frequency was significantly higher in the conservatively managed cysts when compared to the aspirated cysts: total torsion rate (39% vs 12%, p<0.001) prenatal torsion rate (25% vs 4%, p<0.001) and postnatal surgery rate (63% vs 8%, p<0.001, (Figure 2).

The majority of aspirated ovarian cysts were simple at the time of diagnosis. It is known that complex ovarian cysts have a higher likelihood of having already undergone torsion when compared to simple cysts. We therefore performed the same ≥40mm analysis but only included ovarian cysts that the authors stated were simple at diagnosis in the conservatively managed group, and excluded the complex cysts in the aspirated group. In this further analysis, there were 97 cases of simple ovarian cysts ≥40mm that were conservatively managed, and 48 cases ≥40mm in the aspirated group. The higher complication rates still persisted in the prenatal conservatively managed group compared to the aspiration group: prenatal torsion rate 10% vs 0% (p=0.03); total torsion rate 24% vs 8% (p=0.03), postnatal surgery rate 62% vs 8% (p<0.001).

Using the data of only conservatively managed cases with torsion and those that did not undergo torsion, we investigated the ability of the largest prenatally measured diameter of an ovarian cyst to predict torsion through an ROC curve (Figure 3). Although the diagnostic accuracy of the greatest diameter alone was not high it was significant: the area under ROC curve was 0.58 (p=0.045, 95% confidence interval 0.54-0.66). Table 2 outlines the sensitivity and specificity of the ovarian cyst diameter on prenatal ultrasound to predict prenatal torsion.
Discussion

Our findings support the role of prenatal ultrasound guided aspiration of ovarian cysts as a means to reduce rates of fetal ovarian torsion and postnatal surgery. We found significantly lower rates of total torsion in the group of cysts that underwent prenatal aspiration when compared to ovarian cysts treated conservatively that measured between 40-79mm. There was also significantly lower rates of prenatal torsion for cysts measuring 30-59 mm and 70-79mm that were aspirated prenatally. However, due to the low quality of studies included in the analysis the strength of the recommendation remains very low according to the GRADE scoring system. Prenatal aspiration of complex cysts had an at least 50% rate of torsion and no evidence is currently available advocating for its use. Caution is advised in interpreting these data as there were only 4 complex cysts aspirated prenatally in the literature.

Given the available data in the currently published literature, we found evidence that the risk of prenatal torsion increases with size of the cyst at the time of diagnosis. Interestingly, the risk of prenatal torsion was highest in the 50-59mm group followed by the 40-49mm group with the risk declining for larger and smaller cysts. A potential explanation of this finding may be that larger cysts are less mobile within the fetal abdomen and therefore less likely to undergo torsion and that the smaller cysts have a lower intrinsic risk of torsion. The highest rates of total torsion were in the 70-79mm group followed by the 50-59mm group.

In our meta-analysis, the rate of prenatal resolution was only 10%. This may be explained by the persistently elevated hormonal levels in gestation from the pregnant mother. Postnatally, several groups have shown that there is a tendency towards resolution of ovarian cysts within 6-12 months of life, probably due to the decreased hormonal stimulus.
Rates of ovarian loss in complex cysts were variable but high in all the large published series – ranging from 44%-89%. The significance of unilateral ovarian loss in future fertility and endocrine function is particularly difficult to evaluate in the modern age of widespread contraceptive use. Furthermore, studies addressing this topic are scarce and inconclusive.

Heling et al. pointed out that 11% of their patients with complex cysts who underwent surgery did have twisting but nevertheless the ovary was viable. Thus in a small subgroup of complex cysts ovarian salvage is still possible. There is however no reliable way to differentiate torsion from a haemorrhagic cyst apart from an operation. Some groups have also stated a high rate of haemorrhagic conversion at birth, especially with vaginal delivery – these cases saw higher rates of isolated haemorrhage rather than torsion in their cysts. Regarding simple cysts, Galinier et al. concluded that they do not require surgical intervention. However, they also reported that 51% of those simple cysts converted to complex cysts, and that the total rate of ovarian loss in their complex series was 86.5%. Similarly, Bagolan et al. reported that 21% of their simple cysts converted to complex and underwent torsion.

The effectiveness of ovarian cyst aspiration in neonates is also unclear, as there are no large case series using this treatment method. Some authors have stated that it may prevent unnecessary operation, however others have observed that re-accumulation of the cyst fluid often occurs requiring multiple interventions. One study found 1 in 5 of their patients required a second aspiration. Re-accumulation of fluid is also a risk with prenatal aspiration – one study found that 10 of 14 antenatally had a recurrent cyst in the follow-up US. Therefore, when counselling the parents, clinicians should be aware that the only definitive form of treatment is surgery and that cysts aspirated pre- or postnatally should be monitored for fluid re-accumulation.

Although rare, other complications of fetal ovarian cysts are noteworthy. There have been several publications of haemorrhage into the cyst significant enough to cause fetal anaemia requiring transfusion.
or delivery.25,26 Another case report described displacement of thoracic organs due to the sheer size of the cyst, which had grown to 100mm by the 30th week of gestation, and prenatal aspiration was employed.27 Jeanty et al. identified 19 cases in the literature who presented postnatally with bowel obstruction and were found intraoperatively to have a mobile ovarian cyst thought to have caused inflammation and adhesions.29 The risk of a persistent autoamputated cyst has not been compared to the risk of laparoscopy in causing adhesions, and there is diverging opinion regarding the management of these cases.29,30 Finally, there has been one case in the published literature of an asymptomatic infant with bilateral ovarian torsion at elective postnatal surgery who was found antenatally to have bilateral ovarian cysts.99

Limitations and risk of bias

There have been no randomised controlled trials on the management of fetal ovarian cysts, and all studies identified were case series with high heterogeneity and risk of bias. There was some variability in the outcomes reported and a high degree of variability on the management pathways of the different included studies. A comprehensive assessment of the studies included using the QUADAS-2 tool is summarised in Supplementary Figure 1. The frequency of prenatal ultrasound scans, timing of postnatal investigations and indications for postnatal surgery differed greatly between the studies.

Publication bias is a significant risk in the aspirated cases. Most (32 of 56) of the patients treated by prenatal aspiration were treated in one of two centres, and the small number of publications did not allow for a funnel plot to be generated. Confounding factors, namely clinical expertise, could also have lead to better results in these two centres.

Another key factor is the accuracy of prenatal diagnosis. Bagolan et al. excluded 5 (7%) patients from their study due to inaccurate prenatal diagnosis. Other studies have also shown that definitive diagnosis is not
always possible by prenatal US.\textsuperscript{14} This is relevant as the accuracy of diagnosis of the observed cysts is unlikely to have been 100%. Furthermore, this uncertainty may add to the risks when performing prenatal aspiration, albeit allowing for the confirmation that the cyst is indeed of ovarian origin, by cytological examination and measurement of fluid estradiol and progesterone concentration. Prenatal aspiration for purely diagnostic purpose is not advocated by any group.

Finally, the majority of published studies have not described the obstetric or fetal complications associated with prenatal aspiration or conservative management, and simply stated that no complication was observed. Gestational ages at birth were not always described in studies, which would have allowed an assessment of the risk of preterm birth in either comparison group. One study did provide gestational ages at birth of their 13 patients treated by prenatal aspiration and found the median gestation age at birth to be 40 weeks with a range of 35 to 41 weeks.\textsuperscript{4} Risks to the fetus include haemorrhage and injuring nearby structures, as well as accumulation of the cyst. Further studies need to be carried out in order to better quantify the adverse events associated with both management options.

\textbf{Conclusion}

Risk of total and prenatal torsion is associated with size with the highest risk seen in cysts of 40-59mm at the time of diagnosis. In simple cysts greater that 40mm there is a significantly lower risk of torsion and prenatal torsion in cysts treated with antenatal aspiration.

The current body of evidence is made of low quality studies of high heterogeneity and subject to significant biases, especially publication bias. Ideally, management options such as prenatal aspiration need to be studied by randomized controlled studies, as information on procedure safety and adverse
events has been severely lacking. However, the low frequency of these cysts makes this particularly challenging. Thus, a multicentre RCT study would be necessary to confirm the findings that prenatal aspiration significantly decreases the rate of torsion in simple cysts with a diameter measuring greater than 40mm.

Acknowledgments

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<th>References</th>
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deSa D. J. Follicular ovarian cysts in stillbirths and neonates. *Archives of disease in childhood* 1975; 50: 45-50.


Table 1. The frequency of outcomes according to the size group of the cysts. Prenatal torsion is defined as those cysts that were confirmed as torting before birth. Overall torsion is torsion either prenatally or postnatally. Postnatal surgery may have been performed for indications such as torsion, cyst size or complexity, compression of abdominal organs or ruling out malignancy.

<table>
<thead>
<tr>
<th>Cyst Size (mm)</th>
<th>Number of Cysts</th>
<th>Overall Cyst Resolution (%)</th>
<th>Prenatal Cyst Resolution (%)</th>
<th>Prenatal Torsion (%)</th>
<th>Overall Torsion (%)</th>
<th>Postnatal Surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>31</td>
<td>27 (87)</td>
<td>8 (26)</td>
<td>1 (3)</td>
<td>3 (10)</td>
<td>3 (10)</td>
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<tr>
<td>30-39</td>
<td>79</td>
<td>53 (67)</td>
<td>16 (20)</td>
<td>12 (15)</td>
<td>16 (20)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>40-49</td>
<td>96</td>
<td>39 (41)</td>
<td>4 (4)</td>
<td>26 (27)</td>
<td>37 (39)</td>
<td>50 (52)</td>
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<td>15 (34)</td>
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<td>80-110</td>
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<td>1 (9)</td>
<td>2 (18)</td>
<td>2 (18)</td>
<td>9 (82)</td>
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<td><strong>Total Prenatal Conservatively Managed</strong></td>
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<td><strong>148 (46)</strong></td>
<td><strong>34 (10)</strong></td>
<td><strong>66 (20)</strong></td>
<td><strong>102 (31)</strong></td>
<td><strong>158 (49)</strong></td>
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<tr>
<td><strong>Total Prenatal Aspirated Ovarian Cysts</strong></td>
<td><strong>56</strong></td>
<td><strong>46 (82)</strong></td>
<td><strong>13 (23)</strong></td>
<td><strong>2 (4)</strong></td>
<td><strong>6 (11)</strong></td>
<td><strong>4 (7)</strong></td>
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</table>
Figure 1. A – The frequency of total torsion (prenatal or postnatal) according to ovarian cyst diameter. B The frequency of prenatal torsion according to ovarian cyst diameter. * P value < 0.05 indicates the comparison between the frequency of total torsion or prenatal torsion in each ovarian cyst size group and the respective frequency in the aspiration group. Error bars show the ± 95% confidence interval.
Figure 2. A comparison of the frequency of outcomes in cysts greater than or equal to 40mm treated conservatively or by prenatal aspiration.
Figure 3. ROC curve for the performance of the greatest diameter of an ovarian cyst on prenatal ultrasound for prenatal torsion.
Table 2. The sensitivity and specificity of the greatest cyst diameter at the time of diagnosis for prenatal torsion

<table>
<thead>
<tr>
<th>Greatest Diameter (mm)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<td>100</td>
<td>3</td>
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