The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis

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STUDY QUESTION: Does surgical treatment of endometriomas impact on the ovarian reserve as evaluated with antral follicle count (AFC)?

SUMMARY ANSWER: This meta-analysis of published data shows that surgery for endometrioma does not significantly affect ovarian reserve as evaluated by AFC.

WHAT IS KNOWN ALREADY: Surgical excision of an ovarian endometrioma significantly affects ovarian reserve evaluated with anti-Müllerian hormone (AMH) levels. Data for other reliable markers of ovarian reserve, such as AFC, have not been pooled in meta-analyses.

STUDY DESIGN, SIZE, DURATION: A systematic review with electronic searches of PubMed, MEDLINE and Embase up to April 2014 was conducted to identify articles evaluating AFC before and after surgery for ovarian endometriomas, or before or after surgery for the affected versus the contralateral ovary.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Of the 24 studies evaluated in detail, 13 were included for data extraction and meta-analysis, including a total of 597 patients. The primary outcome at pooled analysis was AFC (mean and SD) for affected ovaries before and after surgery. Secondary outcomes were AFC for the affected ovary versus the contralateral ovary before surgery, and AFC for the operated versus the contralateral ovary after surgery. The data were pooled using the RevMan software by the Cochrane Collaboration. Heterogeneity between studies was based on the results of the $\chi^2$ and $I^2$ statistics. A random-effect model was used for the meta-analysis because of high heterogeneity between studies.

MAIN RESULTS AND THE ROLE OF CHANCE: AFC for the operated ovary did not change significantly after surgery (mean difference 0.10, 95% CI 1.45 to 1.65; $P = 0.90$). Lower AFC for the diseased ovary compared with the contralateral one was present before surgery, although the difference was not significant (mean difference $-2.79$, 95% CI $-7.10$ to $1.51$; $P = 0.20$). After surgery, the operated ovary showed a significantly lower AFC compared with the contralateral ovary (mean difference $-1.40$, 95% CI $-2.27$ to $-0.52$; $P = 0.002$).

LIMITATIONS, REASONS FOR CAUTION: Heterogeneity among the selected studies was high; therefore, limiting the conclusions of the present systematic review.

WIDER IMPLICATIONS OF THE FINDINGS: Ovarian reserve evaluated with AFC is not reduced after surgical treatment of an endometrioma. A lower AFC is present for the affected ovary both before and after surgery. Recently, concerns have been raised as to the reliability of AMH as a marker of ovarian reserve. Based on the present findings, surgical treatment of an endometrioma may be considered safer for the ovarian reserve than previously thought.

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Key words: antral follicle count / endometrioma / endometriosis / laparoscopy / ovarian reserve
Introduction

Ovarian endometriomas are present in 17–44% of patients with endometriosis, and may be associated with infertility, dysmenorrhea and chronic pelvic pain (Gelbaya and Nardo, 2011).

The standard approach to the ovarian endometrioma is laparoscopic excision of the cyst capsule with the stripping technique (Hart et al., 2008). Evidence-based guidelines suggest surgical excision in case of symptomatic or large (>3 cm) endometriomas (Leyland et al., 2010; Dunselman et al., 2014).

Recently, however, concerns have been raised as to the possibility of damage to the ovarian reserve after excision of the endometrioma (Shah et al., 2014). Poorer responses to gonadotrophin stimulation for in vitro fertilization (IVF) have been reported for ovaries which have been subjected to excisional surgery (Nargund et al., 1996; Loh et al., 1999; Somigliana et al., 2003; Shah et al., 2014). A higher premature ovarian failure rate (Busacca et al., 2006) and a younger age at menopause (Coccia et al., 2011) have also been reported after excision of bilateral ovarian endometriomas. Two recent systematic reviews have reported consistent evidence on the reduction of ovarian reserve, evaluated with serum anti-Mullerian hormone (AMH) levels, after excisional surgery for endometriomas (Raffi et al., 2012; Somigliana et al., 2012). Non-excisional techniques for the surgical treatment of ovarian endometriomas have been suggested by some authors as more respectful of ovarian reserve (Flyckt and Falcone, 2013). However, no study on non-excisional techniques was found in one of the two systematic reviews (Raffi et al., 2012), whereas such studies were intentionally excluded from the second systematic review (Somigliana et al., 2012).

AMH has gained wide popularity as a marker of ovarian reserve as it offers several advantages compared with other markers; it is stable throughout the menstrual cycle and it is relatively independent of the use of hormonal therapy (Practice Committee of the American Society for Reproductive Medicine, 2012; Rosen et al., 2012; Nelson, 2013; Toner and Seifer, 2013; Shah et al., 2014). Although an ever-expanding body of literature is available on the effect of surgical excision of endometriomas on modifications of the levels of AMH, some methodological problems, such as sample instability, have recently emerged and some authors affirm that caution should presently be exercised in the interpretation of AMH levels in the clinical setting (Rustamov et al., 2012; Ledger, 2014; Muzi et al., 2014).

Antral follicle count (AFC) has been demonstrated to be a reliable marker of ovarian reserve, since it correlates significantly with the age-related follicle count decline, and with ovarian response to IVF stimulation cycles (Practice Committee of the American Society for Reproductive Medicine, 2012; Rosen et al., 2012; Nelson, 2013). Compared with AMH, AFC has the advantage of correlating directly with the ovarian reserve of a single ovary. On the other hand, AMH, being a systemic serum marker, expresses the ovarian reserve of both ovaries, where a balancing effect of a healthy ovary may compensate for a reduced ovarian reserve in the contralateral, affected ovary. In the setting of possible damage to the ovarian reserve attributable to the presence of the endometrioma, to its surgical treatment, or to both, AFC may control for the laterality of the disease and therefore be a more accurate marker than AMH.

No systematic review on the use of AFC to evaluate the effect of surgical treatment of endometriomas on ovarian reserve has been published in the literature so far. The aim of the present systematic review and meta-analysis was to answer the question of whether surgery for an ovarian endometrioma has an impact on the ovarian reserve as evaluated by AFC.

Materials and Methods

The present systematic review included all published research articles that evaluated AFC as a marker of ovarian reserve in patients undergoing surgery of ovarian endometriomas and reported comparisons of AFC before and after surgery in the same patients, or before or after surgery for the affected ovary versus the contralateral, unaffected ovary.

All articles reporting complete surgical excision of the endometrioma were included. Articles reporting alternative surgical techniques, such as vaporization or coagulation of the cyst wall, or a combination of the above, were also included. Non-excisional techniques were pooled separately from exciscional techniques in the meta-analysis.

Studies were excluded if reporting surgery for recurrence of endometriomas. Studies were also excluded if medical therapy, either with GnRH analogs or oral contraceptives, was used in the cycle in which AFC measurements were obtained. Articles reporting measurements of AFC obtained at ovulation induction for IVF were included only if an early follicular phase AFC measurement was reported, and if no GnRH agonist or oral contraceptives were used in the induction protocol.

Studies considered were randomized clinical trials (RCTs), prospective controlled studies, prospective cohort studies or retrospective studies. Only articles written in English were included. Proceedings of scientific meetings were not included.

An electronic database search was performed using MEDLINE, PubMed and Embase for the identification of articles published until 30 April 2014, using the combination of the following search terms: endometriosis, endometrioma, endometriotic cyst, ovarian reserve, AFC, laparoscopy, laparotomy, cystectomy, excision, laser, ablation techniques and bipolar coagulation. The above search was conducted independently by three investigators. Following the search, the articles considered pertinent on the basis of the title and abstract were retrieved, and their reference lists were searched for additional potential studies.

Subsequently, three investigators independently read the full text of the pre-selected articles in order to verify the pertinence of the articles to the systematic review on AFC as a marker of ovarian reserve after surgical treatment of ovarian endometriomas. After confirmation of pertinence, studies were excluded if they were reporting an ad interim analysis subsequently published as full report or reporting duplicate data sets. In case of data judged as pertinent but reported in forms not appropriate for meta-analysis, in case of incomplete data or in case of uncertainty on any of the above issues, the authors of the original articles were contacted in order to obtain the information needed.

In the event of disagreement on the inclusion or exclusion of the pre-selected studies for the meta-analysis, or for any other disagreement through the review process as outlined above, consensus was reached after discussion, or after involvement of further investigators. Data from included studies were independently collected by three investigators on standardized forms.

The primary analysis was aimed at evaluation of the change in AFC after surgery, with the primary outcome output expressed as the mean weighted difference in AFC values after surgery compared with AFC values before surgery. Additional analyses were performed to evaluate two secondary outcomes: the difference in mean AFCs between the ovary with the endometrioma and the contralateral, unaffected ovary before surgery and the difference in mean AFCs between the operated ovary and the contralateral ovary after surgery.
As to measurements after surgery, since all studies were reporting different follow-up schedules, it was established that the most prevalent follow-up intervals had to be selected for data pooling. This procedure was intended to reduce the heterogeneity of studies with regard to the different time points at which AFC was measured after surgery.

The data were pooled using the RevMan software (Review Manager version 5.1, the Cochrane Collaboration, 2011). Mean AFC values and SD were extracted from the original articles, or after contacting the authors of the article in case of missing data. Weighted mean differences were calculated for the three different outcomes evaluated. Heterogeneity between studies was based on the results of the $\chi^2$ and $I^2$ statistics. A random-effect model was to be used for the meta-analysis in case of high heterogeneity, whereas a fixed-effect model was to be used in case of low heterogeneity between studies.

**Results**

Twenty-four studies were pre-selected after the electronic search based on article title and abstract, and after manual search of the reference list of the full articles (Fig. 1).

After reading of the full text, a total of 11 studies were excluded. Two studies were excluded because of incomplete data (Coric et al., 2011; Jang et al., 2014); the authors were contacted to identify missing information, but no reply was received. A third study with incomplete data was included after contacting the author, who provided the missing information (Urman et al., 2013). Two studies were excluded since data were reported together for endometriomas and other histotypes, with no subgroup analysis for endometriomas (Candiani et al., 2005; Li et al., 2009). One study (Pados et al., 2010) was excluded because the same set of patients was reported in a second article by the same group (Tsolkidakis et al., 2010). One study was excluded because two different surgical techniques were compared, and results were reported only for one technique versus the other, therefore not meeting the inclusion criteria for any of the three outcomes considered in the present review (Carmona et al., 2011). One study was excluded because AFC measurements were obtained in cycles where therapy with oral contraceptives was administered (Roman et al., 2011). Four of six studies including patients undergoing IVF were excluded for various reasons: one study (Yu et al., 2010) compared AFC for ovaries operated by experienced
versus inexperienced surgeons and another one (Bongioanni et al., 2011) compared operated versus non-operated patients, therefore not meeting the inclusion criteria for any of the three outcomes considered in the present review; a third study (Almog et al., 2010) included patients undergoing a GnRH analog long protocol modified with the addition of pretreatment with oral contraceptives during the measurement cycle and the fourth excluded study (Tang et al., 2013) included patients who had a recurrent endometrioma present at the time of AFC measurements after surgery.

A total of 13 studies were therefore included at final analysis (Donnez et al., 2010; Muzii and Panici, 2010; Tsalakidis et al., 2010; Auber et al., 2011; Biacchiardi et al., 2011; Ercan et al., 2011; Var et al., 2011; Celik et al., 2012; Takashima et al., 2013; Uncu et al., 2013; Urman et al., 2013; Zaitoun et al., 2013; Alborzi et al., 2014), with a total of 597 patients evaluated (Table I).

Three studies were RCTs (Tsalakidis et al., 2010; Var et al., 2011; Zaitoun et al., 2013), eight studies were prospective cohort studies (Donnez et al., 2010; Muzii and Panici, 2010; Biacchiardi et al., 2011; Ercan et al., 2011; Var et al., 2011; Celik et al., 2012; Uncu et al., 2013; Urman et al., 2013; Alborzi et al., 2014) and two were retrospective studies (Auber et al., 2011; Takashima et al., 2013).

Four studies compared two different surgical techniques for the surgical treatment of endometriomas, three with an RCT design (Tsalakidis et al., 2010; Var et al., 2011; Zaitoun et al., 2013) and one with a retrospective design (Takashima et al., 2013). For three of the four studies (Tsalakidis et al., 2010; Var et al., 2011; Takashima et al., 2013), both arms were included in the meta-analysis. Two of these studies (Tsalakidis et al., 2010; Var et al., 2011) compared a complete excision technique versus a non-excisional technique; the patients in which a non-excisional technique was used were considered separately at data pooling. The third study (Takashima et al., 2013) compared two different haemostasis techniques, i.e. bipolar coagulation versus suturing, after laparoscopic cyst excision and were both included in the meta-analysis, although as separate entries. A fourth study (Zaitoun et al., 2013) compared laparoscopic excision versus treatment by laparotomy in an RCT. Since the technique at laparotomy was described as performed with microsurgical techniques and instruments, and therefore different from the laparoscopic technique, the laparotomy arm was not included in the meta-analysis. Two studies (Donnez et al., 2010; Muzii and Panici, 2010) utilized a combination of laparoscopic excision, used for most of the surgical procedure and ablation/coagulation, used for the final part of the procedure; since the stripping procedure was used for removal of 80–90% of the cyst, the procedure was considered as an excisional procedure at data pooling. A retrospective, non-comparative study (Auber et al., 2011), where a non-excisional technique was used, was considered separately at data pooling from studies in which cyst excision was performed.

Nine of the 13 included studies (Tsalakidis et al., 2010; Biacchiardi et al., 2011; Ercan et al., 2011; Var et al., 2011; Celik et al., 2012; Uncu et al., 2013; Urman et al., 2013; Zaitoun et al., 2013; Alborzi et al., 2014) reported data on the preoperative and post-operative values of AFC, with a total of 511 patients included for the evaluation of the primary outcome. As for the secondary analyses, two studies (Biacchiardi et al., 2011; Ercan et al., 2011) reported data on the AFC for the ovary with the endometrioma and the contralateral, unaffected ovary before surgery, with a total of 69 patients. Six studies (Donnez et al., 2010; Muzii and Panici, 2010; Auber et al., 2011; Biacchiardi et al., 2011; Ercan et al., 2011; Takashima et al., 2013) reported data on the operated versus the contralateral ovary at follow-up, with a total of 155 patients.

Follow-up timing schedules varied between the second post-operative day (Ercan et al., 2011) and 9 months after surgery (Biacchiardi et al., 2011), whereas the number of follow-up visits with AFC measurements varied between one (Donnez et al., 2010; Muzii and Panici, 2010; Tsalakidis et al., 2010; Auber et al., 2011; Var et al., 2011; Takashima et al., 2013; Alborzi et al., 2014) and three (Zaitoun et al., 2013) (Table I). All studies reported data at either 3 or 6 months, and these were the intervals selected for meta-analysis in order to reduce bias deriving from different lengths of follow-up. The definition of AFC in terms of diameter of the follicles considered for measurement varied minimally between studies (Table I). Timing of AFC measurement within the cycle, when reported, was consistently in the early follicular phase (Table I). Only one study (Muzii and Panici, 2010) reported blinding of the operator performing the AFC evaluation.

As for the primary outcome measure, i.e. the change in AFC before and after surgical excision of the endometrioma (Fig. 2), no significant change in the mean AFC was observed after surgery (mean difference 0.10, with 95% CI −1.45 to 1.65; P = 0.90). Heterogeneity for this comparison was high (I² = 96%). Patients or ovaries submitted to non-excisional techniques as one of the two arms in an RCT (Tsalakidis et al., 2010; Var et al., 2011) were plotted separately in the meta-analysis (Fig. 3). Also for non-excisional techniques, no significant change in the mean AFC was observed after surgery (mean difference 1.62, with 95% CI −3.78 to 7.03; P = 0.56). Heterogeneity for this comparison was also high (I² = 97%).

As for the secondary outcomes, i.e. AFC for the affected versus the contralateral ovary either before or after surgery, two separate meta-analyses were performed. As to the first additional analysis, i.e. the difference in AFC between the ovary with the endometrioma and the contralateral, unaffected ovary before surgery (Fig. 4), the mean AFC for the ovary with the endometrioma was lower than the contralateral one (mean difference −2.79, with 95% CI −7.10 to 1.51), but statistical significance was not reached (P = 0.20). Heterogeneity for this comparison was high (I² = 90%). As for the second additional analysis, i.e. the difference in AFC between the operated ovary and the contralateral ovary after surgery (Fig. 5), the mean AFC for the operated ovary with excisional techniques was significantly less than the contralateral one (mean difference −1.40, with 95% CI −2.27 to −0.52; P = 0.002). Heterogeneity for this comparison was also high (I² = 71%). A single study (Auber et al., 2011) reported AFC for the operated versus the contralateral ovary after surgery using a non-excisional technique, and was therefore evaluated separately from studies using excisional techniques. In this study, the AFC for the operated ovary (5.8 ± 4.5, mean ± SD) was non-significantly lower than the contralateral, unoperated ovary (6.9 ± 3.4).

**Discussion**

Ovarian reserve tests have been applied to a wide range of clinical scenarios in reproductive medicine (Practice Committee of the American Society for Reproductive Medicine, 2012; Nelson, 2013), including prediction of response to ovarian stimulation for IVF, prediction of age at menopause and monitoring of possible damage to the ovarian tissue.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Mean age ± SD (years)</th>
<th>Mean cyst diameter ± SD (cm)</th>
<th>Unilateral/bilateral</th>
<th>Follow-up timing (months)</th>
<th>Diameter of follicles for AFC measurement (mm)</th>
<th>Day of AFC measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alborzi et al. (2014)</td>
<td>Prospective cohort</td>
<td>193</td>
<td>28.4 ± 5.4</td>
<td>NR</td>
<td>121/72</td>
<td>3</td>
<td>2–10</td>
<td>3–4</td>
</tr>
<tr>
<td>Auber et al. (2011)</td>
<td>Retrospective</td>
<td>10</td>
<td>32.4 ± 6.2</td>
<td>4.8 ± 2.8</td>
<td>10/0</td>
<td>3–5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Biacchiardi et al. (2011)</td>
<td>Prospective cohort</td>
<td>43</td>
<td>34.2 ± 5.4</td>
<td>3.7 ± 1.1</td>
<td>33/10</td>
<td>3, 9</td>
<td>&gt;3</td>
<td>Early follicular</td>
</tr>
<tr>
<td>Celik et al. (2012)</td>
<td>Prospective cohort</td>
<td>65</td>
<td>28.4 ± 5.7</td>
<td>6.4 ± 2.8</td>
<td>46/19</td>
<td>1.5, 6</td>
<td>2–10</td>
<td>3</td>
</tr>
<tr>
<td>Donnez et al. (2010)</td>
<td>Prospective cohort</td>
<td>20</td>
<td>29.2 ± 3.7</td>
<td>4.6 ± 1.3</td>
<td>20/0</td>
<td>6</td>
<td>NR</td>
<td>2–6</td>
</tr>
<tr>
<td>Ercan et al. (2011)</td>
<td>Prospective cohort</td>
<td>36</td>
<td>29.4 ± 4.6</td>
<td>5.2 ± 1.4</td>
<td>36/0</td>
<td>2nd day, 3</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>Muzii and Panici (2010)</td>
<td>Prospective cohort</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
<td>12/0</td>
<td>6</td>
<td>NR</td>
<td>2–3</td>
</tr>
<tr>
<td>Takashima et al. (2013)a</td>
<td>Retrospective</td>
<td>44</td>
<td>36.2 ± 1.9 (Arm a) 35.3 ± 1.6 (Arm b)</td>
<td>6.7 ± 0.9 (Arm a) 6.2 ± 0.7 (Arm b)</td>
<td>44/0</td>
<td>3</td>
<td>2–10</td>
<td>3</td>
</tr>
<tr>
<td>Tsolakidis et al. (2010)</td>
<td>RCT</td>
<td>20</td>
<td>32.8 ± 1.7</td>
<td>3.8 ± 0.5</td>
<td>NR</td>
<td>6</td>
<td>&lt;9</td>
<td>3–6</td>
</tr>
<tr>
<td>Uncu et al. (2013)</td>
<td>Prospective cohort</td>
<td>30</td>
<td>29.0 ± 5.4</td>
<td>4.3 (IQR 3.9–5.2)</td>
<td>15/15</td>
<td>1, 6</td>
<td>2–9</td>
<td>3–5</td>
</tr>
<tr>
<td>Urman et al. (2013)</td>
<td>Prospective cohort</td>
<td>25</td>
<td>32.7 ± 6.1</td>
<td>5.2 ± 1.5</td>
<td>25/0</td>
<td>1, 6</td>
<td>2–10</td>
<td>Early follicular</td>
</tr>
<tr>
<td>Var et al. (2011)</td>
<td>RCT</td>
<td>48</td>
<td>27.0 ± 3.9</td>
<td>4.4 (SD NR)</td>
<td>0/46</td>
<td>6</td>
<td>&lt;9</td>
<td>1–5</td>
</tr>
<tr>
<td>Zaitoun et al. (2013)</td>
<td>RCT</td>
<td>61</td>
<td>24.2 ± 3.1</td>
<td>NR</td>
<td>61/0</td>
<td>6, 12, 18</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>

SD, standard deviation; AFC, antral follicle count; NR, not reported; RCT, randomized controlled trial; IQR, interquartile range.

*aArm a = suture; Arm b = bipolar coagulation.
after conservative surgery, especially for ovarian endometriomas (Nargund et al., 1996; Raffi et al., 2012; Somigliana et al., 2012).

Among other markers of ovarian reserve, AMH and AFC have been shown to best correlate with the pattern of age-related oocyte loss observed histologically (Rosen et al., 2012), and are therefore considered the most reliable non-invasive methods of ovarian reserve evaluation (Practice Committee of the American Society for Reproductive Medicine, 2012; Nelson, 2013).

Surgical excision is considered the most appropriate technique for the treatment of ovarian endometriomas (Hart et al., 2008; Leyland et al., 2010; Dunselman et al., 2014). Recently, however, some concern has been raised as to the possibility that surgical excision of the ovarian endometrioma may negatively impact on the ovarian reserve of the operated ovary. The decrease in the ovarian reserve after surgery may be due to the inadvertent excision of unaffected ovarian tissue together with the diseased tissue (Hachisuga and Kawarabayashi, 2002; Muzii et al., 2002; Muzii et al., 2007).

Evidence of a reduced ovarian reserve has been published in two recent systematic reviews (Raffi et al., 2012; Somigliana et al., 2012), reporting a decrease of the levels of AMH after surgery. In the meta-analysis performed by Raffi et al. (2012), a statistically significant fall of 38% for AMH levels was reported after excisional surgery, with a weighted mean difference of $21.13$ ng/ml (95% confidence interval $21.88$ to $20.37$) following cyst excision. No study was identified for non-excisional techniques. Somigliana et al. (2012), reporting that 9 of the 11 studies included in their systematic review documented a
significant reduction of AMH after excisional surgery, concluded that the evidence from the available literature consistently support a surgery-related damage to the ovarian reserve, and that further evidence to confirm this result is not a research priority.

With regard to the two systematic reviews mentioned above, however, it must be underlined that study heterogeneity was very high for the studies identified. In one of the two reviews, a second analysis limited to the studies with the lowest risk of bias did not reach statistical significance for the effect of surgery on AMH modifications (Raffi et al., 2012). In the other review, a meta-analysis was deemed inopportune due to variability in study designs, reported parameters, lengths of follow-up and different techniques used to measure AMH (Somigliana et al., 2012). Evidence from the published studies on the post-operative decrease in AMH levels after surgery for the endometrioma is therefore still inconclusive, and further studies are necessary to support the association between surgery and decreased ovarian reserve as evaluated with AMH measurements. In addition, concerns have recently been raised as to possible methodological problems with the use of AMH, which may have affected results obtained in published studies (Rustamov et al., 2012; Ledger, 2014; Muzii et al., 2014).

In the present systematic review, ovarian reserve evaluated with AFC was not significantly impaired by surgical excision of the ovarian endometrioma performed with the stripping technique. After surgery, AFC of the operated ovary did not change significantly if compared with the pre-operative values for the same ovary (Fig. 2). Also non-excisional techniques appeared not to affect AFC values after surgery (Fig. 3). Heterogeneity of the included studies was high; therefore, possibly limiting the conclusions of the present systematic review. Study designs and patient inclusion criteria were not homogeneous between the different studies. However, several steps were taken in the present systematic review in order to minimize the risk of bias due to the variability of some parameters. For example, strict inclusion and exclusion criteria were applied for the evaluated studies, the different lengths of follow-up were made uniform by considering only the 3- or 6-month post-operative visit, and the different surgical techniques (excisional versus non-excisional) were analyzed separately.

It may be difficult to explain the different behavior of two reliable markers of ovarian reserve such as AFC and AMH in the evaluation of ovarian reserve after surgical treatment of ovarian endometriomas. Within the context of surgical injury to a single ovary, however, AFC may better reflect the specific injury to the operated ovary, since this marker controls for the laterality of the injury and may therefore be more accurate than AMH. AFC, in fact, directly relates to the ovarian reserve expressed by the single ovary, whereas AMH expresses the ovarian reserve of both gonads, and therefore, in the case of monolateral disease, does not directly reflect the function of the affected ovary. When evaluating surgery-related damage, AFC may therefore be preferred to AMH.

The two meta-analyses performed to evaluate secondary outcomes in the present systematic review compared AFC of the affected ovary with the contralateral healthy ovary in patients with monolateral disease, both before (Fig. 4) and after surgery (Fig. 5). In both comparisons, the affected ovary, either with the endometrioma present before surgery, or after surgical excision, showed reduced AFC compared with the contralateral ovary, by a mean difference of $-2.79$ before surgery $(P = 0.20)$ and of $-1.40$ after surgery $(P = 0.002)$. These data may support the hypothesis of damage to the ovarian tissue that is already present before surgery, and therefore due to the disease itself, and not to the surgical procedure (Muzii and Miller, 2011). Histology analyses of the ovarian cortex surrounding ovarian cysts show that the follicular density in the tissue around the ovarian endometrioma is significantly lower compared with tissue around cysts of other histotypes, such as dermoid or serous cysts (Maneschi et al., 1993), or compared with the contralateral normal ovary (Kitajima et al., 2011), supporting the hypothesis that most of the damage to the ovary after surgery is indeed already present before surgery (Muzii and Miller, 2011). Also, lower AMH values have been reported for patients with the endometrioma present compared with a control group of patients without endometriomas (Uncu et al., 2013). AMH may reflect an immediate insult to the residual ovarian tissue after surgery, which sums up with the ovarian damage provoked by the endometrioma itself (Maneschi et al., 1993; Kitajima et al., 2011). The additional insult provoked by surgery may be, to a certain extent, only temporary, and, in fact, a partial recovery has been reported by some authors at longer follow-up times (Chang et al., 2010; Sugita et al., 2013).

The aim of surgical treatment of ovarian endometriomas is the resolution of pain in case of associated symptoms, and the achievement of a pregnancy in case of associated infertility. Surgery may be indicated also in patients without symptoms, in particular in case of large or suspicious cysts, when malignancy cannot be ruled out unless a surgical specimen is obtained for histology (Muzii et al., 2005). In this view, ovarian reserve modification after surgery is a secondary outcome that should
only be considered after the efficacy of surgical treatment on the presenting symptom(s) has been accounted for. Surgery for the ovarian endometrioma is efficacious when pain or infertility is present (Vercellini et al., 2009; Leyland et al., 2010; Duffy et al., 2014; Dunsilman et al., 2014). The possibility of a reduced ovarian reserve should be discussed with the patient, but this issue should not however change the well-defined indications to surgery, especially when the evidence supporting damage to the ovarian reserve are inconclusive or inconsistent, as is the case for surgery for the ovarian endometrioma.

In conclusion, surgery for the endometrioma has been associated with impaired ovarian reserve. Systematic reviews on AMH as a marker for the reduced ovarian reserve, however, have highlighted the heterogeneity of the published studies and the difficulty in pooling the data (Raffi et al., 2012; Somiglina et al., 2012). AFC may be a more specific marker of ovarian reserve related to surgery, since it controls for laterality of the possible damage. In the present systematic review and meta-analysis, AFC did not appear to change significantly after surgery. The affected ovary had lower AFC both before and after surgery. Further research is required to better clarify the role of the endometrioma per se or of surgical excision in the determination of damage to the ovarian reserve. Additional studies with a direct comparison of AMH and AFC in a long-term follow-up are needed in order to better clarify the role of both markers in the assessment of the impact of surgery on the ovarian reserve. RCTs with adequate sample sizes are necessary to compare different surgical techniques. Investigation of the impact of surgery for the endometrioma on ovarian reserve should still be considered a research priority in reproductive medicine.

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