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Review Article

Effect of Surgery for Endometrioma on Ovarian Function

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ABSTRACT Endometriosis affects a significant proportion of reproductive-aged women. The impact of the disease on ovarian function is an important consideration when planning treatment in women who want to retain the potential of future childbearing. This review will specifically address the association between endometriomas and diminished ovarian reserve, with a particular focus on the impact of surgical endometrioma resection on ovarian function. The existing literature supports an adverse effect of ovarian endometriomas on spontaneous ovulation rates, markers of ovarian reserve, and response to ovarian stimulation, although data on clinical pregnancy and live birth rates remain inconsistent. Surgical removal of endometriomas may worsen ovarian function by removing healthy ovarian cortex or compromising blood flow to the ovary. It is evident that surgical excision of endometriomas acutely impairs ovarian function as measured by ovarian reserve markers; whether this represents progressive or long term impairment remains the subject of ongoing investigation. Journal of Minimally Invasive Gynecology (2014) 21, 203–209 © 2014 AAGL. All rights reserved.

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Endometriosis is estimated to affect 1 in 10 women of reproductive age in the United States [1]. The disease has been described as having three distinct forms: superficial endometriotic implants (peritoneal endometriosis), ovarian cysts lined with endometrioid mucosa (endometriomas), and solid masses of endometriotic, adipose, and fibromuscular tissue between the rectum and vagina (rectovaginal endometriotic nodules) [2]. The detrimental effect of endometriosis on fertility is well established in advanced cases, in which severe adhesive disease impairs tubal motility and ovum pickup; however, the mechanisms that underlie the association between mild endometriosis and infertility remain unknown [3].

Whether identification of an endometrioma warrants its excision in the subgroup of women undergoing infertility treatment remains a subject of ongoing debate. Multiple factors feed into the decision tree, such as size of the ovarian cyst, appearance of the cyst on ultrasound, presence of associated pain, benefit or harm to future fertility treatments, and recurrence or primary incidence. On the basis of available research, the 2005 European Society of Human Reproduction and Embryology guidelines recommend laparoscopic ovarian cystectomy in cases of endometriomas >4 cm before in vitro fertilization (IVF), to provide histologic diagnosis, reduce risk of infection, and improve access to follicles [4]. However, a 2010 Cochrane review concluded that, compared with expectant management, endometrioma excision has no additional beneficial effect on clinical pregnancy rates or number of oocytes retrieved [5]. Many practitioners reserve surgery for women with concomitant symptoms of pain and proceed directly to IVF to reduce overall time to pregnancy in most other cases. Further investigation is required insofar as the most appropriate treatment for endometriomas in various subpopulations of women with the disease.

The present review specifically addresses the association between endometriomas and diminished ovarian reserve, with particular focus on the effect of surgical endometrioma resection on ovarian function.

The authors declare no conflicts of interest.

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Effect of Endometriomas on Ovarian Reserve

Before discussing the effect of endometrioma resection on ovarian function, it is important to establish whether the presence of an intact endometrioma affects ovarian reserve. Several authors have used clinical outcomes such as spontaneous ovulation rates and response to gonadotropin stimulation during ovulation induction or IVF as an approximation of ovarian response.

Women with ovaries containing endometriomas seem to have a lower spontaneous ovulation rate. Benaglia et al [6] demonstrated this in a prospective study that evaluated 70 women with unsurgically monitored unilateral endometriomas by sonographically tracking the laterality of ovulation. Assuming an equal ovulation rate for healthy and affected ovaries, the authors identified a 31% lower ovulation rate in women with ovaries containing endometriomas ($p = .002$) [6]. The dimensions of the cysts did not have a role in whether there was a diminution in ovulation. Cysts <30 mm or >29 mm equally led to lower ovulation rates. There also seems to be reduced responsiveness to gonadotropin stimulation as well as lower baseline levels of the ovarian reserve marker anti-müllerian hormone (AMH) [7] in the presence of endometriomas, although the data are inconsistent. Somigliana et al [8] assessed the response to gonadotropin simulation in 36 women with unilateral endometriomas without previous surgery who underwent 56 IVF–intracytoplasmic sperm injection (ICSI) cycles. The mean (SD) number of follicles >15 mm in intact ovaries was 4.0 (2.2), and in affected ovaries was 3.0 (1.7) ($p = .01$) [8]. A 2006 meta-analysis also showed a lower number of follicles after controlled ovarian stimulation in patients with endometrioma as compared with control subjects ($p = .002$), although the clinical pregnancy rate did not significantly differ between the 2 groups [9]. These findings have not been supported, however, by several more recent studies of IVF outcome in women with unilateral unsurgically treated endometriomas that failed to demonstrate a difference in total follicular number or size, gonadotropin dosage, or number of oocytes retrieved when comparing affected with unaffected ovaries [10–12]. The most recent of these studies demonstrated that women with unilateral endometriomas ≤3 cm in diameter who underwent IVF-ICSI had comparable numbers of oocytes retrieved from ovaries with endometriomas and contralateral normal ovaries (5.9 [4.3] vs 5.4 [3.8]; not significant) [10]. Of note, none of these studies included oocyte quality in the analysis. The authors speculated that the discrepant results may be related to undersampling in earlier studies and/or selection bias due to individual patients contributing multiple cycles to the analysis.

One limitation to the studies evaluating clinical ovarian responsiveness in patients with unsurgically treated unilateral ovarian endometriomas is the possibility of the compensatory effect of the healthy ovaries. To control for this limitation, several studies have evaluated ovarian responsiveness in patients with unsurgically treated bilateral endometriomas. Reinblatt et al [13] demonstrated that the presence of bilateral endometriomas does not affect embryo quality, although the study was limited by a small sample size of only 13 women. Embryo quality was defined by the authors of that study as good, fair, or poor (for further details, please refer to Reinblatt et al [13]). In a more recent multicenter retrospective cohort study that evaluated IVF outcome in women with unsurgically treated bilateral endometriomas, ovarian responsiveness based on the total number of developing follicles was significantly decreased in women with bilateral endometriomas as compared with control subjects (mean [SD], 9.6 [3.3] vs 14.1 [6.8]; $p < .001$). However, the quality of the oocytes retrieved and the clinical pregnancy rate were not affected [14].

Another limitation of these studies is lack of histologic confirmation of endometriosis. Previous histologic studies have compared ovarian cortex specimens from patients with endometriomas against those with other benign ovarian cysts [15] or mature teratomas [16] and have shown lower follicular density in ovarian cortex surrounding endometriomas. A recent study by Kitajima et al [17] compared cortical biopsy specimens from ovaries containing small endometriomas with contralateral unaffected ovaries and found that follicular density was significantly lower in cortex from ovaries with endometriomas than in the unaffected contralateral cortex (mean [SD], 6.3 per mm^3 [4.1 per mm^3] vs 25.1 per mm^3 [15.0 per mm^3; $p = .002$).

Surgical Resection of Endometriomas and Ovarian Reserve

Multiple studies have explored the effect of surgical resection of endometriomas on ovarian reserve. A key factor in analyzing the literature is the method of assessing ovarian reserve used by various authors. For example, Horikawa et al [18] examined the ovulation rate in 28 infertile women with unilateral endometriomas using a retrospective crossover study to evaluate the effect of ovarian cystectomy. They demonstrated that the ovulation rate was significantly decreased in the affected ovary after laparoscopic cystectomy as compared with before surgery (mean [SD] 16.9% [4.5%] vs 34.4 [5.5%]; $p = .01$) [18]. Although that study suggested an adverse effect of surgery on ovarian function, the end point of ovulation alone provides limited information about long-term ovarian function. Inasmuch as ovarian reserve cannot be directly measured, the most common approach uses surrogate serum markers such as AMH and follicle-stimulating hormone (FSH), sonographic markers such as antral follicle count (AFC) and ovarian volume, or clinical markers including response to gonadotropin stimulation during ovulation induction or IVF. More recently, a few authors have also examined the issue via ovarian histology.

Serum Markers

An extensive and still expanding body of literature on the effect of endometrioma resection uses serum AMH as a primary marker of ovarian reserve. In this regard, AMH offers several advantages as a simple marker for testing ovarian reserve [19]: it is stable throughout the menstrual cycle [20–22], corresponds well with the AFC [23,24], and correlates well with age-related changes in ovarian response [25].

In a 2012 meta-analysis, Somigliana et al [26] evaluated changes in serum AMH concentration after surgical excision of ovarian endometriomas. In 10 of the 11 studies, stripping enucleation of the cyst wall was performed. Eleven studies were included in the analysis, and 9 of these showed a statistically significant reduction in serum AMH after surgery. The 2 studies that failed to demonstrate any significant modification in serum AMH were published by the same group of researchers [27,28]. Although it is difficult to account for these discrepant results, the authors propose multiple potential explanations including differences in surgical skill, differences in study population, or changes in the AMH concentration due to the storage process (i.e., differences in storage temperature between centers). A second meta-analysis published by Raffi et al [29] in the same year also looked at the effect of endometrioma on ovarian reserve using AMH as a marker. That analysis demonstrated a statistically significant postoperative decrease in circulating AMH in a pooled analysis of 237 patients from 8 studies (weighted mean difference, 1.13 ng/mL; 95% confidence interval [CI], –0.37 to –1.88).

Several studies have examined whether the initially demonstrated decrease in serum AMH after endometrioma resection persists in the extended postoperative period. Several authors have demonstrated a significant and persistent decline in serum AMH concentration at 3 months [30], 6 months [31,32], 9 months [33], and up to 12 months [34] after laparoscopic cystectomy to treat an endometrioma. The most recent cohort study, published in 2013 by Uncu et al [35], evaluated the effect of endometriomas and their removal on ovarian reserve as determined using serum AMH concentration and AFC preoperatively and at 1 and 6 months after surgery. Thirty women who underwent laparoscopic excision of endometriomas $\geq$2 cm were age matched with 30 healthy women without ovarian cysts. As compared with control subjects, women with endometriomas had significantly lower AMH concentrations at baseline (mean [SD], 2.8 [2.2] ng/mL vs 4.2 [2.3] ng/mL; $p = .02$) and exhibited a further decrease at 6 months postoperatively (1.8 [1.3] ng/mL vs 2.8 [2.2] ng/mL; $p = .02$).

Contrary to these findings, a few authors have identified recovery of AMH concentration as soon as 1 month after laparoscopic cystectomy. While noting a similar decrease in median AMH concentration at 1 week postoperatively (2.23 ng/mL vs 0.67 ng/mL), Chang et al [36] also identified subsequent recovery of AMH concentration at 1 month (1.14 ng/mL; $p < .05$) and 3 months (1.50 ng/mL). A longer prospective study observed patients who underwent cystectomy to treat endometriomas for 1 year and noted an initial decline in serum AMH concentration in all patients, followed by partial recovery in 50% [37]. Histologic analysis of the pathology specimens revealed a statistically significant difference in the number of follicles removed at surgery between the group with recovery of serum AMH concentration compared with the group in which the decline persisted, which suggested a potential mechanism for the discrepant findings in the literature on this topic.

Many of the studies that examined AMH concentration after endometrioma resection also studied other markers of ovarian reserve as secondary end points, including FSH, estradiol, and AFC. The results are inconsistent, which may be related to the greater sensitivity of AMH in this capacity. For example, the meta-analysis by Raffi et al [29] showed a significant postoperative decrease in circulating AMH but no significant reduction in the secondary end point of AFC, which the authors attributed to beta error due to small sample size. Similarly discrepant findings between AMH and AFC have been demonstrated by others [34,35], and several studies have failed to show any significant differences between preoperative and postoperative values of FSH, luteinizing hormone, estradiol, and inhibin B [31,33,34]. In contrast, Ercan et al [28] did not document a significant reduction in serum AMH, ovarian volumes, or Doppler indices after surgical stripping of endometriomas, but did note a reduction in AFC in the surgically treated ovary compared with the contralateral ovary in the third month (mean [SD], 3.7 [2.1] vs 6.4 [2.7]; $p < .50$).

Response to Gonadotropin Stimulation

Gonadotropin stimulation during IVF has also been used as a measure of ovarian function after surgical excision of endometriomas; however, it remains unclear whether impairment in response to stimulation after surgery to treat endometrioma affects the end outcomes of pregnancy and live birth rates. A group of studies have examined the IVF outcome in women who underwent surgical excision of endometriomas compared with control patients with tubal factor infertility. Overall results from these studies have been inconsistent, with several showing no difference in pregnancy rates [38–41], and a few demonstrating a reduction [42,43]. Demirol et al [44] recently published a prospective randomized study that evaluated the effect of endometrioma cystectomy on IVF outcome. Ninety-nine patients with unilateral endometriomas 3 to 6 cm in diameter were included and randomized to either a group that underwent ovarian cystectomy before IVF-ICSI or a group that underwent IVF-ICSI directly. As compared with those who proceeded directly with IVF-ICSI, women who underwent ovarian surgery to treat endometrioma underwent substantially longer stimulations, required substantially higher dosages of recombinant FSH, and had a substantially lower mean number of mature oocytes retrieved; however, there was no observed difference in fertilization or pregnancy rates [44]. These findings were supported by nonrandomized data noting higher gonadotropin requirements [45] and lower numbers of mature oocytes retrieved [46] in women with surgically treated vs nonsurgically treated endometriomas; however, no difference in pregnancy rates was observed between the 2 groups.

One possibility for the discrepancy is that many studies did not differentiate between unilateral and bilateral disease, which does not control for the ability of a healthy contralateral ovary to compensate for the affected ovary [47]. This limitation was overcome in subsequent studies that used the same patients and compared follicular development in surgically and nonsurgically treated ovaries; however, data remain inconsistent [48–54]. Among the most recently published studies is a retrospective evaluation of 93 women who underwent surgical excision of unilateral endometriomas before IVF that demonstrated complete absence of follicular growth in 12 surgically treated ovaries with gonadotropin stimulation [55]. However, data were limited by small sample size and lack of correlation with pregnancy rates.

Histologic and Sonographic Markers

The inadvertent removal of ovarian cortex while stripping the wall of the endometriotic cyst from the unaffected ovary is thought to be one mechanism by which endometrioma resection may result in diminished ovarian reserve. A few authors have attempted to characterize and quantify this effect using histologic, molecular, or sonographic markers of ovarian reserve. In a prospective study of 42 women undergoing laparoscopic cystectomy for treatment of benign ovarian cysts, histologic analysis revealed that excision of cysts with well-defined capsules such as dermoids and cystadenomas resulted in inadvertent removal of healthy ovarian tissue in only 6% of patients as compared with 54% after excision of endometriomas ($p \leq .005$) [56]. Other authors have supported the greater loss of ovarian tissue after resection of endometriotic as compared with nonendometriotic cysts [57], with identification of ovarian cortex containing primordial follicles in as many as 69% of pathologic specimens after laparoscopic endometrioma resection [58].

Similar findings have been demonstrated in studies evaluating residual ovarian volumes after laparoscopic removal of endometriomas. Exacoustos et al [59] showed significantly lower residual ovarian volumes after surgical excision of endometriomas (mean [SD], 19.9 [17.8] cm^3 vs 5.1 [3.2] cm^3; $p < .001$), but no difference after excision of dermoid cysts (10.1 [11.4] cm^3 vs 6.7 [3.3] cm^3; not significant). The thickness of ovarian parenchyma removed was directly proportionate to the cyst diameter in a retrospective series of 35 patients ($p = .02$), and normal ovarian tissue was noted in 97% of the specimens [60]. Of interest, a study that observed serial AMH levels after laparoscopic excision of endometriomas in 65 women failed to identify a correlation between AMH level and histopathologic analyses of removed ovarian tissue [30], which suggested that removal of ovarian tissue is not the only mechanism involved in the decrease in ovarian function after surgical excision of endometriomas. There is limited evidence of additional damage from vascular compromise after electrosurgical coagulation. Doppler studies of the ovarian artery showed a decreased mean pulsatility index (1.59 vs 2.17; $p = .001$) and mean resistance index (0.73 vs 0.81; $p = .001$) after surgical excision of endometriomas [61].

Special Considerations

Bilateral Endometriomas

A few studies have focused specifically on the effect of surgery on ovarian reserve in a subgroup of women with bilateral endometriomas. Somigliana et al [62] compared IVF cycle outcomes in 68 women who had undergone cystectomy for treatment of bilateral endometriomas with 136 controls with sonographic evidence of endometriosis and found lower numbers of oocytes retrieved and lower rates of clinical pregnancy (odds ratio, 0.34; 95% CI, 0.12–9.92) and live births (odds ratio, 0.23; 95% CI, 0.07–0.78) after endometrioma resection. A 2012 systematic review of serum AMH concentrations after endometrioma excision published by the same group included a subset of 5 studies that evaluated serum AMH concentrations in women who underwent surgery to treat bilateral endometriomas [24]. Four of the 5 studies documented a statistically significant 2- to 3-fold postoperative reduction in AMH concentration [31,36,63,64], and 1 study noted no difference [27]. A second 2012 meta-analysis by Raffi et al [29] also involved a subgroup analysis of bilateral endometriomas using 2 studies with 32 patients. A trend toward a greater decrease in serum AMH concentration was noted in women who underwent surgery to treat bilateral endometriomas as compared with unilateral endometriomas (weighted mean difference, –1.18 ng/mL [95% CI, 1.07 to –3.34] vs –0.96 ng/mL [95% CI, –0.22 to –1.70]), although results in the group with bilateral endometriomas did not achieve statistical significance, likely due to small sample size.

Recurrence of Endometriomas After Surgery

Another consideration is the potential for endometrioma recurrence after surgical excision. Investigators have postulated that an ovary in which the primordial follicular pool is depleted after surgical endometrioma excision has less potential for development of recurrent disease, based on the premise that endometriomas originate from ovulatory events. Paradoxically, endometrioma recurrence may therefore be viewed as a favorable marker of increased potential for ovarian responsiveness. Somigliana et al [65] investigated this hypothesis in a retrospective series of 45 women who previously had undergone unilateral endometrioma excision. Ovarian response was compared in those who did and did not experience disease recurrence, with significantly higher number of follicles identified in the ovaries with vs without recurrent endometriomas (mean [SD], 2.5 [2.3] vs 1.1 [1.5]; $p < .05$). Several limitations of that study include the small sample size and inability to differentiate between incomplete resection of the endometrioma at the original surgery and true recurrence.

Surgical Technique for Endometrioma Resection

Given the evolving data about the potentially detrimental effect of surgical excision of endometriomas on ovarian reserve, it is possible that surgical technique is a critical component of preserving ovarian function. Of several surgical techniques for endometrioma excision, the 3 most common include stripping the cyst wall from the surrounding ovarian cortex, cyst drainage, and thermal ablation or coagulation.

Two randomized clinical trials and a meta-analysis favor the stripping technique for endometrioma excision over thermal ablation [66–68]. These studies demonstrated that stripping the cyst wall from the surrounding ovarian cortex resulted in less postoperative pain, reduced disease recurrence, and higher rates of spontaneous pregnancy. On the basis of these results, a 2008 Cochrane review concluded that excision of endometriomas, rather than ablation, should be the preferred surgical approach to facilitate spontaneous pregnancy and minimize risk of recurrence [68]. There was thought to be insufficient evidence insofar as the best surgical technique, however, in subfertile women who may undergo planned infertility treatment [68].

In subfertile women, ovarian reserve, rather than recurrence of pain, may be the better outcome by which to evaluate the various surgical approaches to endometrioma resection. Several studies have demonstrated a diminished effect on ovarian reserve with cyst drainage and vaporization or thermal coagulation as compared with cyst excision. In one study, 20 patients with endometriomas were randomized to undergo laparoscopic cystectomy or the three-step procedure including laparoscopic drainage, administration of gonadotropin-releasing hormone analogues for 3 months, and laparoscopic laser vaporization [34]. A greater reduction in mean serum AMH concentration was noted in the cystectomy group as compared with the 3-step approach (3.9 to 2.9 ng/mL vs 4.5 to 3.9 ng/mL; $p = .03$). In another randomized trial, Var et al [69] evaluated the effect of surgical technique on ovarian reserve determined by AFC and number of dominant follicles and retrieved oocytes after controlled ovarian hyperstimulation. Forty-eight women were randomized to undergo either endometrioma stripping or drainage and bipolar coagulation. This was followed by IVF, and embryo transfer was performed in 37 of 48 patients. The AFC was significantly reduced after cystectomy compared with coagulation (mean [SD], 3.7 [1.3] and 4.8 [0.6]; $p = .001$), as was ovarian volume (6.3 [1.95] and 9.87 [2.01]; $p = .01$). Of the women that underwent IVF, ovarian response to ovulation induction was statistically reduced in the cystectomy group as measured by the number of oocytes retrieved (3.1 [0.8] vs 3.9 [0.9]; $p = .01$). These findings have been supported in 2 retrospective studies that demonstrated a similar postoperative reduction in ovarian volume and AFC after cystectomy when compared with cyst ablation using plasma energy [70,71].

The method of achieving hemostasis after cystectomy has not been shown to affect IVF outcome. In a single recent study, Takashima et al [72] compared the effects of bipolar electrocoagulation vs suture placement after laparoscopic excision of endometrioma and found no significant differences in serum concentrations of AMH or FSH between either group in the samples obtained before and after surgery. Furthermore, there were no differences in IVF outcome between the 2 surgical methods.

An alternate operative technique proposed and evaluated by Donnez et al [73] is partial cystectomy with removal of 80% to 90% of the endometrioma combined with carbon dioxide vaporization of the remaining cyst wall closest to the hilus. Analysis of 20 women with unilateral endometriomas showed similar ovarian volume (mean [SD], 7.45 [2.93] cm^3 vs 7.82 [3.91] cm^3) and AFC (5.5 [2.4] vs 5.7 [1.6]; $p = .001$) in the ovary operated on compared with the ovary not operated on when assessed at 6 months after the initial surgery.

In conclusion, the existing literature supports an adverse effect of ovarian endometriomas on ovulation rates, markers of ovarian reserve, and response to ovarian stimulation, although data on clinical pregnancy and live birth rates remain inconsistent. Surgical removal of endometriomas may worsen ovarian function by removing healthy ovarian cortex or compromising blood flow to the ovary. It is evident that surgical excision of endometriomas acutely impairs ovarian function as measured by ovarian reserve markers. Whether this represents progressive or long-term impairment is unclear.

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