The Endometrioma Treatment Paradigm When Fertility Is Desired

Charles E. Miller, MD FACOG

Professor, Obstetrics & Gynecology - Department of Clinical Sciences, Rosalind Franklin University of Medicine and Science, North Chicago, IL USA

Director, Minimally Invasive Gynecologic Surgery, Advocate Lutheran General Hospital, Park Ridge, IL USA

Address for correspondence:

Dr. Charles Miller

120 Osler Drive, Suite 100

Naperville, IL 60540 USA

(630) 364-1119 – phone

(866) 477-4910 - fax

chuckmillermd@gmail.com

The author did not receive any financial interest or support in the preparation of this manuscript.

The Endometrioma Treatment Paradigm When Fertility Is Desired: A Systematic Review

ABSTRACT

Objective

To establish an endometrioma treatment paradigm (decision tree) in the treatment of the ovarian endometrioma through the review of current literature.

Data Source

A thorough literature search including PubMed, Google Scholar and the Cochrane Library was performed from April 2020 – July 2020. The review was completed by utilizing the following key words:

- Endometriosis and Pain (pre and post-surgery)
Endometriosis and Infertility (pre and post-surgery)

Endometriosis and ART (with and without surgery)

Endometriomas and IVF (with and without surgery)

Effect of endometriomas on implantation

Effect of endometriomas on antral follicle count (pre and post-surgery)

Evaluating the complex ovarian cyst (to rule out malignancy)

Resistive index in evaluation of the ovarian cyst

Endometriosis and BCL6

All relevant articles were assessed. The references of the assessed articles were then reviewed, and if pertinent, evaluated (figure 1).

Methods of Study Selection

Articles published in English that addressed the endometrioma in regards to the following were included:

1. Diagnosis
2. Treatment of pain based on size and/or surgical intervention.
3. Treatment of fertility based on size and/or surgical intervention.
4. Surgical technique.
5. IVF success based on size and/or surgical intervention.
6. Risk of rupture at time of egg retrieval.
8. Impact on implantation.

Tabulation, Integration, Results
Fifty-six articles were included in this systematic review. While conducting this literature review, several themes were noted. In general, the literature on the ovarian endometrioma appears to be homogeneous in regards to imaging the endometrioma, excision rather than desiccation for endometrioma ≥ 3 cm causing pain and/or infertility, minimal use of bipolar energy at time of ovarian surgery, and risk of severe infection secondary to inadvertent rupture of cysts during egg retrieval. Conversely, studies on ovarian endometrioma are much more heterogeneous in terms of surgery and ART; that is, whether surgery should be performed. Certainly, an endometrioma ≥ 5 cm should be excised prior to ART. Moreover, it appears that antral follicle count and implantation may be enhanced with surgery.

**Conclusion**

By completing an extensive literature review, an easy to use algorithm for the diagnosis, evaluation, and treatment of endometriomas was developed to help clinicians in their treatment of endometriosis patients in the short and long term.

**Introduction**

Early in my career, Dr. Arthur Haney, Division Director of Reproductive Endocrinology and Infertility at Duke University at the time, told me, “Always remember, the ovary is unforgiving”. It was such a simple statement, yet so profound. Insufficient treatment of an ovarian endometrioma increases risk of recurrence, overzealous treatment can negatively impact ovarian reserve with resultant concern for fertility and hormonal well-being.

The purpose of this systemic review of the literature was to create an algorithm to help surgeons define when surgery is the most appropriate treatment for an ovarian endometrioma.
A treatment paradigm for an endometrioma was developed by incorporating interactive presentations from the 48th Global Congress of the AAGL in 2019 and the 5th Edition of the EndoDubai Congress held in February of 2020, as well as medical literature. The basis of the decision tree is a series of clinical questions. In addition, various surgical techniques for the treatment of the ovarian endometrioma are discussed.

Question #1 – Is there concern for ovarian malignancy?

Given its high sensitivity and ease of access, transvaginal ultrasound has become the gold standard for the diagnosis of ovarian cysts and thus, the ovarian endometrioma. The endometrioma is considered a complex cyst, typically presenting as a unilocular cyst, at times multilocular, with a typical homogenous ground glass appearance.\(^1\text{-}^3\)

In a 2008, multicenter study, Timmerman and colleagues evaluated 1,066 patients with 1,233 persistent adnexal tumors via transvaginal grayscale and Doppler ultrasound; 27% were malignant tumors, while 73% of the masses were benign. Information on 42 grayscale ultrasound and six Doppler variables was collected and evaluated to determine which variable had the highest predictive value for a malignant tumor and for a benign mass – the IOTA Rules.\(^4\)

Five simple rules were selected that best predict malignancy (M-rules) as follows:

- Irregular solid tumor
- Ascites
- At least four papillary structures
- Irregular multilocular solid tumor with a greatest diameter greater than or equal to 100 mm
- Very high color content on Doppler exam
The following five simple rules suggest that a mass is benign (B-rules):

- Unilocular cyst
- Largest solid component less than 7 mm
- Acoustic shadows
- Smooth multilocular tumor less than 10 mm
- No detectable blood flow with Doppler exam

Unfortunately, despite a sensitivity of 93% and a specificity of 90% and positive and negative predictive values of 80% and 97%, these ten simple rules were applicable to only 76% of tumors.

Although low, 0.8% - 0.9% (0.8%, 95% CI: 0.4-1.6%) (0.9%; 95% CI: 0.4-16%) (95% CI: 4.1-15.3), there is a risk of occult malignancy in women with a history of suspected or known endometriotic cysts. Thirteen ovarian cancer case-controlled studies demonstrated a significantly increased risk of low grade serous cancers and endometroid invasive cancers in patients with endometriosis.5-7

In a meta-analysis published by Pearce including 13,226 controls, 7,911 with invasive cancer and 1,907 borderline ovarian cancer patients, self-reported endometriosis was associated with a significantly increased risk of low grade serous cancers (31 [9·2%] of 336 cases, 2·11, 1·39–3·20, p<0·0001), endometrioid invasive cancers (169 [13·9%] of 1220 cases, 2·04, 1·67–2·48, p<0·0001), and clear cell carcinoma (136 [20·2%] of 674 cases vs 818 [6·2%] of 13,226 controls, odds ratio 3·05, 95% CI 2·43–3·84, p<0·0001).8 No association was noted between endometriosis and risk of mucinous, high grade serous invasive ovarian cancers, or borderline ovarian malignancies, serous or mucinous subtype.
According to The American College of Obstetricians and Gynecologists, Practice Bulletin, Number 174, November 2016, consultation with or referral to a gynecologic oncologist is recommended for a premenopausal woman with a very elevated CA125 level and ultrasound findings suggestive of malignancy or if there is an elevated score on a formal risk assessment such as the IOTA Rules. If, ultimately, ovarian function is maintained, egg/embryo cryopreservation should be performed early on, given potential for recurrence.9 (figure 2).

Question #2 – Does the patient have significant pain?

Current literature certainly suggests that pelvic pain in women with ovarian endometrioma is actually associated with coexisting peritoneal lesions. In 2012, Chapron, reported findings on 300 consecutive patients with histologically proven ovarian endometrioma and significant preoperative pain.10 Following multiple logistic analysis, uterosacral ligament involvement was associated with a high severity of chronic pelvic pain and deep dyspareunia. Intestinal involvement was related to increasing dysmenorrhea; while vaginal endometriosis was associated with a higher incidence of lower urinary tract pain.

Khan also demonstrated that pelvic pain in women with ovarian endometrioma is mostly associated with coexisting peritoneal lesions.11 In this study, 269 endometrioma patients with peritoneal lesions were compared to 81 patients with endometrioma and no lesions. If peritoneal lesions were noted, 85.4% experienced pain, while pain was noted in 38.3% of those without peritoneal involvement.

If a patient with an endometrioma and pain is to be treated surgically, it is important to consider technique. Beretta noted symptom recurrence in 9.5 months in the group treated by fenestration and coagulation, while the cystectomy group noted symptom recurrence at 19
months. Symptom recurrence at two years was noted to occur in 56.7% of the fenestration and coagulation group and only 15.8% of the cystectomy group, in the Alborzi study. Furthermore, reoperation occurred in 22.9% of the fenestration and coagulation group, but only 5.8% of the cystectomy group.\textsuperscript{12-13} In both studies, despite greater pain improvement in the cystectomy group, the drainage and coagulation group also noted pain relief post-surgery.

While there is no medical therapy that effectively treats existing endometriomas, consider medical therapy to mitigate recurrence or when the endometrioma is less than 4 cm to decrease pain symptoms.\textsuperscript{14-16} Despite the tendency to excise the endometrioma at time of surgery, one must remember that small endometriomas likely do not impact pain and aggressive “stripping” could negatively alter ovarian function. Thus, if surgery is to be performed, egg/embryo cryopreservation should be considered, ideally, prior to surgery (figure 3).

Question #3 – Is the endometrioma impacting spontaneous pregnancy?

According to guidelines from the European Society of Human Reproduction and Embryology (ESHRE) 2005, the American Society for Reproductive Medicine (ASRM) 2012 and the National Health Service (NHS) 2010, laparoscopic cystectomy via excisional surgery for an endometrioma greater than or equal to 4 cm is felt to improve fertility (spontaneous pregnancy) compared to drainage and coagulation.\textsuperscript{17-19}

Beretta (1998) and Alborzi (2004) demonstrated the advantage of cystectomy versus drainage and coagulation in randomized controlled trials.\textsuperscript{12-13} As can be seen in table one, cumulative pregnancy rate was superior in the cystectomy group (table 1).
In a 2016 JMIG publication, comparing plasma energy and cystectomy, Mircea noted similar pregnancy rates at 24 months (61.3% versus 69.3%) and 36 months (84.4% versus 78.3%) in a multicenter case controlled study involving 104 patients with endometrioma greater than 3 cm.\textsuperscript{20}

One, again, must consider the negative impact on ovarian health and the ovarian reserve subsequent to surgery. Therefore, egg/embryo freezing should be considered pre surgery or secondary to recurrence, post operatively (figure 4).

Question #4 – Is the endometrioma negatively impacting success with IVF?

Thus far, there has been little debate regarding this decision tree. However, whether to perform egg retrieval prior to surgery is hotly contested. In 2014, the European Society of Human Reproduction and Embryology (ESHRE) Guideline Development Group recommended that clinicians only consider cystectomy prior to ART to improve endometriosis-associated pain or the accessibility of follicles.\textsuperscript{16} In a small study, published in 2014 by Coccia, 52 women with endometrioma less than 3 cm undergoing IVF were compared to 12 women with endometrioma greater than 3 cm.\textsuperscript{21} While follicles greater than 16mm, retrieved oocytes, mature oocytes and transferred embryos were similar, implantation rate was 50% less in the larger endometrioma group (6.5% vs. 13%) and pregnancy rate was also less (16.7% vs. 26.2%).

Including two recent meta-analysis, literature is replete noting decreased AMH for 6-9 months post-surgery.\textsuperscript{22-29} Uncu noted progressive decline in AMH was worse with bilateral endometrioma, but not statistically significant.\textsuperscript{23} In a study of 193 women, Alborzi saw significant decrease in AMH for up to nine months, with decline more significant with bilateral
endometriomas; others agree. In a 2014 study published in Fertility and Sterility, Kwon noted significant AMH decline with bilateral endometriomas, or if endometrioma size is 5 cm or greater. Multiple other publications note the negative impact of endometrioma, greater than 5 cm, on fertility.

Mechanisms have been proposed to why cystectomy can worsen ovarian reserve. This includes removal of normal ovarian cortex, thermal damage to ovarian parenchyma and ovarian vasculature and finally, inflammation secondary to surgery. In 2010, Roman published a retrospective study on 35 women who underwent excision of an ovarian endometrioma. A direct proportional relationship was noted between endometrioma size and ovarian parenchyma removed at surgery. Matsuzaki, in 2009, noted that normal ovarian tissue along with the excised endometrioma was 10 times more frequently noted than with other cyst types. This appears to be a greater concern in younger women who, according to Romualdi in 2011, have even greater follicle reduction with smaller endometriomas excised.

In 2012, Somigliana published a comprehensive systematic review regarding excision of endometriomas and ovarian reserve, in particular, AMH. Nine of the eleven studies documented a significant reduction of AMH; post-surgery. Decline most evident in women undergoing bilateral endometrioma surgery. Interestingly, ten of the eleven series utilized bipolar energy event though it is associated with greater risk of ovarian devascularization and thus, negatively impacting AMH. Peters performed a systematic review of the impact of suturing versus surgical energy on ovarian function. Of the 8 studies reported, 62.5% noted superior conservation of AMH with suture; 37.5% showed no difference. Four studies with
suture showed no change in postoperative AMH, while 4 other studies with suture demonstrated a 15% - 31% decrease. Seven of 8 studies with energy (mainly bipolar) noted a 27% - 53% decrease in AMH from baseline.\textsuperscript{35} Ata performed a systematic review and meta-analysis, including 3 randomized controlled trials and one prospective study, comparing suture, hemostatic sealant, and bipolar desiccation. Hemostatic sealant and suturing were associated with a mean decline in AMH that was 6.95% less (95% CI, −13.0% to −0.9%; \( p = .02 \)) at three months.\textsuperscript{36} Small feasibility studies have provided early data indicating success as measured by antral follicle count with the use of plasma energy or laser vaporization for treatment of the ovarian endometrioma.\textsuperscript{37-38} Moreover, a 2015 prospective, cohort pilot study utilizing ethanol sclerotherapy for 15 minutes noted only a 5.9% recurrence rate.\textsuperscript{39}

In 2015 Somigliana published a multi-analysis evaluating conservative management of ovarian endometriomas and IVF.\textsuperscript{31} While follicle numbers were similar, on both the affected and non-affected side, the endometrioma, in general, were less than 3 cm. Yang performed a meta-analysis in 2015, incorporating some of the same studies as Somigliana, while adding three other studies.\textsuperscript{40} In the 9 studies cited, incorporating 1,039 cases, the number of oocytes retrieved (mean difference [MD] −1.50; 95% CI, −2.84 to −0.15, \( p = 0.03 \)), metaphase II (MII) oocytes retrieved (MD −3.61; 95%CI −4.44 to −2.78, \( P < 0.00001 \)) and total embryos formed (MD −0.66; 95% CI −1.13 to −0.18, \( P = 0.007 \)) were significantly lower in the endometrioma group. However, the number of good quality embryos, embryo implantation rate, and clinical pregnancy rate were similar. Again, most endometrioma were less than or equal to 3 cm.

In a meta-analysis published in 2015, incorporating five controlled studies, 655 patients, similar live birth clinical pregnancy, miscarriage, cycle cancellation, and follicle production was noted.
comparing surgical and conservative treatment. The surgical arm was associated with decreased antral follicle count, eggs retrieved, and higher doses of gonadotropins.\textsuperscript{41} Furthermore, Ferrero et al. did find a significant reduction in follicle numbers - $4.8 \pm 2.0$ versus $2.6 \pm 1.3$ (73.1%; 95% C.I., 52.2–88.4%), oocytes retrieved -$4.2 \pm 1.7$ versus $2.0 \pm 1.2$ (80.8%; 95% C.I., 60.6–93.4%) and good quality oocytes - $3.7 \pm 1.5$ versus $1.5 \pm 1.1$ (76.9%; 95% C.I., 56.4–91.0%) when endometrioma was greater than or equal to 5 cm at time of IVF/ICSI.\textsuperscript{42} One must consider potential drawbacks of conservative management. Firstly, women with ovarian endometrioma can experience a faster progressive decline in AMH levels. Kasapoglu compared AMH levels measured at six month intervals in 40 women with endometrioma to 40 age-matched controls in their 2018 retrospective longitudinal study.\textsuperscript{43} The endometrioma group not only had a lower baseline AMH than the control group, $2.83 \text{ (0.70–4.96) ng/mL}$ versus $4.42 \text{ (2.26–5.57) ng/mL}$, but also noted a greater percentage of decline $26.4\% \text{ (11.36–55.41\%)}$ versus $7.4\% \text{ (-11.98, 29.33\%)}$ at 6 months. Twenty two women with endometriomas had antral follicle counts measured at recruitment and at six months; decrease was noted from 10 (8–12) to 8 (6.3–10). Loss of follicular density can occur secondary to stretching of the ovarian cortex. Gonadotoxic insult can result from free iron uptake from cells near the endometrioma. As focal inflammation due to the endometrioma, can occur in the ovarian cortex leading to fibrosis and loss of cortex specific stroma. This inflammation, associated with reduced vascularization and increased oxidative stress may lead to atresia and resultant antral follicle count reduction. With excision, there may be reduction or even reversal of the endometrioma’s damaging effects.
Tao in 2017, published a meta-analysis including 21 published studies - 2,649 ART cycles (CI): [0.13, 1.82], P =0.0007), as well as a meta-analysis by Nickkho-Amiry in 2018, revealed no difference in pregnancy rate [5 studies, OR 0.88 (95% CI 0.60, 1.29)] and live birth rate [4 studies, OR 0.75 (95% CI 0.54, 1.06)]. Tao again noted increased gonadotropin dosage, and significant reduction in number of dominant follicles and total number of oocytes retrieved in the cystectomy group. Finally, Laursen, included one randomized controlled trial and nine retrospective studies, again noting no differences in odds ratio of live birth 0.87 (95% CI 0.64–1.18) (figure 5).

At present, there appears to be no consensus regarding necessity of endometrioma prior to IVF. However, as will now be discussed, there are special circumstances when ovarian cystectomy should be considered. Perhaps in the future, studies comparing non-treatment versus treatment of endometriomas 3 cm or greater without use of bipolar energy, will show an advantage to surgery.

**Question #5 – Is there risk of endometrioma rupture at time of egg retrieval?**

Due to the size and/or position of the endometrioma, egg retrieval may be more difficult. Benaglia, noted the frequency of non-complete follicular aspiration more than three times higher with endometriomas (OR 3.6, 95% CI 1.4 to 9.6). Additionally, accidental contamination of follicular fluid can occur, which lowers fertilization rate and pregnancy rate. Finally, and most problematic, rupturing an endometrioma at time of egg retrieval can lead to increased risk of pelvic infection and or abscess (figure 6).
**Question #6** – Does the endometrioma negatively impact the antral follicle count on the affected side in comparison to the non-affected side?

Some investigators recommend evaluation of antral follicle count (AFC) as opposed to AMH, as it allows direct comparison between the ovary with, and without endometrioma.\(^{49}\)

Almog evaluated the impact of different cyst types on AFC, noting that the endometrioma significantly lowers AFC (7.5 ± 0.7 versus 9.3 ± 0.9), when compared to the unaffected side.\(^{50}\)

Ozugur saw not only significantly lower AFC on the endometrioma side, but lower median number of oocytes retrieved (11.5 versus 13.5).\(^{51}\)

Kasapogul raised concerns with progressive decline in ovarian reserve over time, noting a 26.4% decrease in AMH at 6 months, versus 7.4% in controls and AFC declining from 10 to 8.\(^{43}\) Pados noted an increase in AFC 36 months post-surgery. Especially when AFC is low on the endometrioma side, cystectomy should be considered prior to ART\(^{52}\) (figure 7).

**Question #7** – Does the endometrioma increase risk of implantation failure?

For this discussion, implantation failure includes women with recurrent pregnancy loss as well as unexplained infertility. Simón in 1994, noted that embryos created from donated oocytes, originating from donors with endometriomas exhibited a significantly lower implantation rate.\(^{53}\)

He believed this was secondary to an alteration of the oocyte.

Endometriosis is an inflammatory condition, and inflammation has been shown to alter endometrial receptivity.\(^{54-55}\) Endometriosis is associated with increased local and systemic cytokine expression, which has a negative effect on normal endometrial function. Monsanto noted that surgical removal of endometriosis altered the local and systemic effect of these cytokines.\(^{56}\)
In a 2017 article, Lessey highlighted literature illustrating that endometriosis is a progesterone resistant disease leading to a blunted or inadequate response to progesterone in both eutopic and ectopic endometrial cells; ultimately disrupting endometrial normalcy.\textsuperscript{57} He then cited literature describing how progesterone resistance associated with endometriosis, contributes to increased cell proliferation and survival, as well as elevated levels of estrogen receptor. Furthermore, because progesterone plays a role in decreasing inflammation and estrogen increases inflammation, a proinflammatory condition secondary to progesterone insensitivity occurs. A role in endometriosis related implantation failure has also centered on the defects of decidualization. This change in endometrial morphology, that is decidualization, is essential for pregnancy success.\textsuperscript{58-59}

While these effects may not be related to the endometrioma per se, laparoscopic endometrioma removal and excision of endometriosis may be required in women desiring fertility (figure 8).

**Conclusion**

When a persistent complex ovarian cyst is noted on ultrasound, the ovarian endometrioma treatment paradigm (decision tree) can be utilized to incorporate prevailing literature in the decision making process. This includes not only whether to operate, recommended technique of surgery indicated, and whether egg/embryo freezing is recommended, but also by asking one or more of the following questions:

1. Is there concern for ovarian malignancy?
2. Does the patient have significant pain?
3. Is the endometrioma decreasing spontaneous pregnancy?
4. Is the endometrioma negatively impacting success with IVF?
5. Is there risk of endometrioma rupture at time of egg retrieval?
6. Does the endometrioma negatively impact the antral follicle count on the affected side in comparison to the non-affected side?
7. Does the endometrioma increase risk of implantation failure?

The advantages and disadvantages of the surgical treatment of the ovarian endometrioma can be evaluated based on current clinical experience.

If surgery is to be performed on the ovarian endometrioma, cystectomy when compared to drainage and coagulation, yields a higher pregnancy rate and post-operative pain improvement.

Use of plasma energy or laser vaporization may prove to be advantageous. Bipolar should not be used for hemostasis, rather if necessary, proceed with suturing versus use of a hemostatic sealant.24, 35, 56


Figure Legend:

**Figure 1 – Flow Diagram**
Figure 2: Malignant potential

Figure 3: Pain
Figure 4: Impacting spontaneous pregnancy

Figure 5: Negatively impacting IVF success
Figure 6: Risk of endometrioma rupturing

Figure 7: Negatively impacting antral follicle count
Figure 8: Recurrent implantation failure

Table 1: Pregnancy rate - cystectomy vs. drainage and coagulation

<table>
<thead>
<tr>
<th>YEAR</th>
<th>PATIENTS</th>
<th>OBSERVATION TIME</th>
<th>CUMULATIVE PREGNANCY RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beretta 1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cystectomy ≥ 3 cm</td>
<td>64</td>
<td>2 years</td>
<td>66.7%</td>
</tr>
<tr>
<td>• Drainage and Coagulation</td>
<td></td>
<td></td>
<td>23.5%</td>
</tr>
<tr>
<td>Alborzi 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cystectomy ≥ 3 cm</td>
<td>100</td>
<td>1 year</td>
<td>59%</td>
</tr>
<tr>
<td>• Drainage and Coagulation</td>
<td></td>
<td></td>
<td>23%</td>
</tr>
</tbody>
</table>