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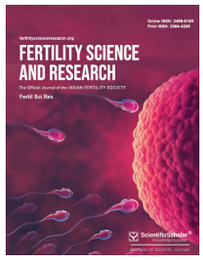


*Review Article*

# Endometrioma and Infertility

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## ABSTRACT

Endometrioma is common in young women. They often present with pain or infertility. Treatment can be medical or surgical. Various treatments are discussed, and the pros and cons are analysed.

**Keywords:** ART, Cystectomy, Endometrioma, Infertility, Pain

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Endometriosis, the implantation of endometrial tissue outside the uterus, is a common gynaecological problem affecting young women. The incidence rate of endometriosis is 1.36 per 1000 person-years.[1] Interestingly a systematic review observed that the frequency of endometriosis in studies varies geographically. It was found to be 1.4% in the European studies, 5.7% in the US studies and the highest was 15.4% in the Asian studies.[2] In women with infertility, the pooled prevalence of endometriosis was found to be 23.8%.[3] The lesions of endometriosis are usually seen in the ovaries, peritoneum, and fallopian tubes and can be deep or superficial with varied degrees of adhesions. The cystic lesion formed in the diseased tissue affected by endometriosis is called an endometrioma or chocolate cyst. They are most commonly seen in the ovary. Ovarian endometrioma, seen in 17%–44% of women with endometriosis, is usually associated with pelvic pain and infertility.[4] In 19%–28% of patients, the endometriomas are bilateral.[5]

## PATHOPHYSIOLOGY

Ovarian endometrioma is characterised by the presence of metaplastic smooth muscle cells, which arise from the metaplastic endometrial stromal cells or ovarian stromal cells located at the site of the endometriosis.[6] These cells are fully functional and show increased levels of oxidative stress with dysregulation of reactive oxygen species. This disruption leads to increased cellular proliferation and activation, which in turn results in cellular fibrosis and metaplasia of smooth muscle cells present in the ovarian tissue.[7]

Ovarian endometriomas seen in endometriosis are often associated with deep peritoneal lesions (70.5%). In a study, it was seen that 98.4% of endometriomas had dense adhesions with the broad ligament, with 70.5% of endometriotic lesions having deep infiltration and 29.5% of endometriotic lesions having superficial infiltration.[8] Redwine,[9] observed that women with ovarian endometriosis had a higher incidence of intestinal and pelvic endometriotic lesions. Hence, the presence of an endometrioma usually points to extensive endometriosis disease.

Endometriomas are usually asymptomatic initially. As they grow in size, they can cause dysmenorrhea, dyspareunia, dyschezia and chronic pelvic pain. At times large endometriomas can rupture spontaneously and present as acute abdomen. Malignant transformation has also been reported in endometriomas.[10] Endometriosis has a 4.2 times risk of developing ovarian cancer. This risk is maximum with deep infiltrating endometriosis and ovarian endometriomas. Endometrioid, clear cell, mucinous, and low-grade serous type ovarian cancers are more commonly seen in them than in high-grade serous ovarian cancer. Transvaginal ultrasonography and magnetic resonance imaging are the tools that aid in the diagnosis of endometriosis. Laparoscopy remains the gold standard for diagnosing endometriosis.

## ENDOMETRIOMA AND INFERTILITY

The cause of infertility in women with endometriosis is not definite. The chronic inflammation and fibrosis seen in endometriosis often result in disturbed folliculogenesis, leading to premature follicular recruitment, increased follicular loss and poor quality of remaining follicles.[11]

In younger women aged <35 years, the number of follicles observed in the normal ovarian tissues was persistently lower in women with endometrioma than with other non-endometriotic cysts, as seen in a study by Kuroda M *et al.*[12] The relative density of follicles in the presence of an endometrioma compared to other cysts was found to be 35.4% at 20 years, 46.8% at 30 years and 62.7% at 35 years. Above the age of 35 years, the relative density of follicles was found to be similar in both endometriotic and non-endometriotic cysts. The study reflects the damaging effect endometrioma has on the ovarian reserve in younger women.[13]

The relationship of anti-Müllerian hormone (AMH) with endometrioma is controversial. Women with endometrioma experience a progressive decline in serum AMH levels, which is faster than that seen in healthy women.[13] Prior surgery on the ovary and the age of the patient have a negative impact on the AMH level, as seen in a study by Streuli *et al.*[14] Many studies have shown that antral follicular count (AFC) is low in women with endometrioma.[15–18] This can be attributed to the presence of inflammation[19] or the anatomic distortion causing difficulty in counting follicles.[20] Lima *et al.*[21] in their study observed a lower AFC count in endometrioma without a change in oocyte retrieval, pointing to a possible error in the counting of follicles due to difficult visualisation. On the other hand, a systematic review concludes that AFC remains identical in women with or without endometrioma.[22]

## TREATMENT

Treatment of endometrioma depends on whether pain or infertility is the presenting symptom for which relief is sought. It can be medical or surgical.

## MEDICAL

Medical management of endometrioma is done for symptomatic pain relief and to decrease the size of the endometrioma. Nonsteroidal anti-inflammatory drugs and neuromodulators like anticonvulsants, selective serotonin uptake inhibitors, and antidepressants are often used for pain relief, either alone or together.

Dienogest (DNG) is the most commonly used hormonal treatment for endometrioma. It is used in a dose of 2 mg per day for relief of symptoms, mainly pain. A study [23] showed that continuous intake of DNG results in a 66.71% decrease in the mean volume of endometrioma at 6 months and 76.19% at 12 months. A 74.05% reduction in dysmenorrhea was seen after 6 months of treatment, which further improved with a reduction to 96.55% at 12 months. DNG also decreased dyspareunia and chronic pelvic pain in 42.71% and 48.91% of women after 6 months and 51.93% and 59.96% after 12 months, respectively.

Kizilkaya[24] also observed a similar reduction in the size of endometrioma and relief of symptoms with oral DNG.

In addition to DNG, oral contraceptive pills (OCPs), gonadotropin-releasing hormone agonists (GnRHa), norethindrone acetate, norethindrone acetate with aromatase inhibitor, or danazol are the other drugs used to reduce the size of ovarian endometriomas. A meta-analysis [25] showed a significant reduction in the cyst diameter (reduction 1.32 cm, 95% CI, 0.91–1.73) and volume (1.35, 95% CI, 0.87–1.83) with DNG. Similar, significant reductions were seen with the OCP (1.06 cm, 95% CI, 0.59–1.53), GnRHa (1.17 cm, 95% CI, 0.42–1.92), norethindrone acetate (0.6 cm, 95% CI, 0.27–0.94), and danazol (1.95 cm, 95% CI, 1.18–2.73). Norethindrone acetate with aromatase inhibitor was also effective in reducing endometrioma volume.

The reduction in the size of endometrioma was the greatest with DNG and norethindrone acetate plus the aromatase inhibitor letrozole, followed by GnRHa and relugolix, a gonadotrophin receptor antagonist.[26] The volume reduction was not statistically significant with combined hormonal contraceptives or other progestins.

The role of expectant management vs. hormonal treatment for endometrioma was evaluated in a study.[27] Patients on hormonal treatment showed a reduction in the size and number of endometriomas on serial magnetic resonance imaging when compared with patients on expectant management. It is hence advocated to start medical treatment to contain endometriomas and to avoid surgery.

## SURGERY

Surgery is the most common treatment offered for endometrioma and relief of its symptoms.[28] Surgical treatment of endometrioma

includes laparoscopic cystectomy with stripping of the cyst wall, cyst drainage and ablation, and sclerotherapy. Surgery is the preferred treatment modality for relief of chronic pain. In women desiring pregnancy, its role is debatable.

Since endometriomas are usually found close to the ovarian cortex, where primordial follicles are located, cystectomy for endometrioma can result in significant loss of ovarian tissue.[29] Unlike endometriomas, benign ovarian cysts are usually located away from the ovarian cortex, and cystectomy in them does not decrease ovarian reserve. Vascular injury of the hilar region of the ovary during surgery and the energy source used for haemostasis can lead to ischaemia and affect ovarian function.

A fall in serum AMH levels done in the postoperative period in patients with cystectomy was reported by Younis *et al*.[30] However, the antral follicle counts were not affected, suggesting that AMH levels provide a better assessment of the risk of loss of the ovarian reserve in patients with endometrioma.

Serum AMH of large endometriomas is significantly lower than small endometriomas post laparoscopic cystectomy. No significant differences were noted in the AFC between the small and large endometrioma preoperatively and 1 month postoperatively in a study.[31] The fall of serum AMH post cystectomy was more in bilateral endometrioma (57%) than in unilateral endometrioma (39.5%) postoperatively.[32] Similar results showing a decrease in AHM levels in bilateral endometriomas and endometriomas greater than 7 cm have been observed by Moreno *et al*.[33] Endometrioma surgery has a deleterious effect on short-, medium- and long-term post-operative AMH levels.

A meta-analysis done by Ata *et al*.[34] observed that the excision of endometrioma using bipolar electrocoagulation negatively affects ovarian reserve when compared with other haemostatic methods. They found that the use of haemostatic sealants and sutures during cystectomy has less adverse effect on the ovarian reserve compared to bipolar coagulation. The decrease in serum AMH levels was 6.95% less with alternative haemostatic methods than with bipolar coagulation at 3 months post-surgery. Similar results have been observed in other studies.[35,36]

The effect of bipolar coagulation on ovarian reserve was compared in patients with endometriomas and benign ovarian cysts in a study.[37] No significant change in AMH levels or AFCs was observed in women with benign ovarian cysts with bipolar coagulation or nonthermal haemostasis. Lower postoperative AMH and AFCs were seen in women with endometrioma when electrocoagulation was used as compared to nonthermal haemostasis.

Donnez *et al*.[38] described a combined approach in which cystectomy was done for 80%–90% of endometrioma and laser ablation was used for 10%–20% of cysts close to the hilus to reduce ovarian loss. Park *et al*.[39] suggested that electrocoagulation surgery with bipolar current might have a greater impact on the ovarian reserve in patients with endometriomas, which are often characterised by pelvic adhesions.

These studies advocate avoidance or minimal use of bipolar electrocoagulation during laparoscopic excision of endometrioma to preserve ovarian reserve in women desiring pregnancy.

The ablative procedure for endometrioma includes draining the contents of the endometrioma followed by the destruction of the cyst wall. A meta-analysis compared the effect of cystectomy and ablation done for endometrioma on ovarian reserve.[40] It was seen that there was a considerable fall in the AMH levels in both groups. A significant fall in AFC counts was seen in the cystectomy group compared to the ablation group, which showed no fall at 6 months. The study suggests that both ablation and cystectomy negatively affect the ovarian reserve, as seen by a fall in AMH; however, this damage was marginally less by ablation, as indicated by AFC. Paik *et al*.[41] also obtained similar results but said that the recurrence rate was higher in the ablation group.

The depth of the endometriotic tissue is usually around 0.6 mm. Caution should be exercised while ablating the cyst wall to prevent inadvertent injury to the ovarian tissue. Various techniques like bipolar diathermy, laser and plasma energy have been utilised for ablation. Compared to bipolar diathermy, laser and plasma energy achieve a more superficial effect, tissue-sparing, thus minimising the inadvertent damage to the underlying ovarian parenchyma.

The role of carbon dioxide ($CO_2$) laser vaporisation for the treatment of endometrioma was studied by Candiani M *et al*.[42] They observed that antral follicle count increased in women undergoing treatment with $CO_2$ laser vaporisation when compared to cystectomy. Serum AMH levels were reduced in the cystectomy group and remained unchanged in laser vaporisation post-3-month follow-up. The study points out that the $CO_2$ laser used to treat endometrioma is associated with minimal damage to ovarian tissue.[42] Another meta-analysis which compared laser vaporisation with laparoscopic cystectomy found no difference in pregnancy and recurrence rates in both procedures.[43] However, they observed a lower antral follicle count in the laparoscopic cystectomy group.

Sclerotherapy is a nonsurgical option for the treatment of ovarian endometriomas. It involves injecting ethanol, a sclerosing agent, into the cyst cavity, which can be either removed or left inside the cyst. The sclerosing agent affects the cells lining the cyst wall, resulting in inflammation and fibrosis of the cyst wall and finally causing obliteration of the cyst. A systematic review showed that sclerotherapy

improved pain in 68%–96% of women with endometrioma, with a recurrence rate of 0%–62.5%.[44] They observed that the number of oocytes retrieved during in vitro fertilisation (IVF) cycles was more after sclerotherapy for endometrioma as compared with laparoscopic cystectomy. No difference in the oocyte retrieval nor the pregnancy rates was noted between the two groups. Also, AFC and serum AMH levels were unaffected post sclerotherapy in women with endometrioma. A similar result was observed by Alborzi *et al.*[45] in their study. They stated that recurrence, however, was more in patients treated with sclerotherapy.

The safety of sclerotherapy as a treatment for endometrioma was studied by Miquel *et al.*[46] They reported complications in 13/131 (9.9%) transvaginal ethanol sclerotherapy procedures. Nine patients had minor complications, one patient had a pelvic infection, two patients had ovarian abscesses and one patient had ethanol intoxication, which required treatment. They concluded that transvaginal ethanol sclerotherapy is a successful and useful alternative to cystectomy surgery for endometrioma with minimal ovarian damage. Adequate precautions must be taken to prevent, identify and treat complications, if any.

## ART

Studies have been done to evaluate the role of surgery prior to assisted reproductive technology (ART). A retrospective study was done by Bongioanni *et al.*[47] on 254 women undergoing IVF. Of them, 112 patients had a cystectomy done for endometrioma prior to ART, and 142 patients did not undergo any surgery.

Significantly lower antral follicular count during ART was noted in women who had cystectomy for endometrioma than in women who had not undergone surgery (11.7 and 16.9, respectively). In addition, women who had cystectomy required more amount of follicle stimulating hormone (FSH) for ovarian stimulation than those without cystectomy (3298 and 2339, respectively, $p < 0.001$). The ovum retrieval, serum oestrogen levels, implantation rate, pregnancy rate and live birth rate were identical in the two groups.

Raffi *et al.*[48] conducted a study to evaluate the impact of surgery for endometrioma on long-term reproductive outcomes in women. They included 68 women who underwent either open or laparoscopic cyst excision, drainage, ablation, or unilateral oophorectomy and compared it with 68 healthy women. 50% (19/38) of women in the surgical group desirous of pregnancy were able to conceive spontaneously, and 4 of them conceived again with ART. Eight patients conceived with ART post-surgery. They found a pregnancy rate of 71% post-surgery for endometrioma. Pregnancy rates in the control group were as high as 98%. They observed that the average age of menopause was 48 years in the study group and 49 years in the control group.

Sukur *et al.*[49] evaluated the impact of surgery for endometrioma in women undergoing ART. They studied 26 women who underwent ART with ovarian endometrioma and 53 women who underwent ART post-surgery. They found live birth rates of 23.7% in the surgery group and 26.1% in the control group, which was not significant; however, a higher cycle cancellation (13.7% vs. 0%) was seen in the surgery group. Cycle cancellation may be due to hyporesponsiveness of the ovary, follicular dysplasia or low quality of the ovum obtained.

Xin Tao,[50] in their meta-analysis, observed that the dose of gonadotropin required for ovarian stimulation was significantly higher in the women with endometriomas who underwent cystectomy. In addition to this, the serum oestrogen measured on the day of human chorionic gonadotropin (hCG) administration, the number of dominant follicles obtained and the number of retrieved oocytes were considerably lower in them. Cystectomy of endometrioma did not affect the length of stimulation, the pregnancy rate and the live birth rate.

Wu *et al.*,[51] in their meta-analysis, reported similar live birth rates per cycle between 11.8% and 37.9% in the post-surgery group compared to 16.1%–42.6% in the expectant group. Miscarriage rates were 7.6%–25% in the surgery group and 10%–28.6% in the expectant group. Cycle cancellation was more in the surgery group than the expectant group (6.3%–47.1% vs. 1.5%–35.5%, respectively). Similar results were seen in studies comparing surgery versus no treatment prior to ART.[22,52,53] GnRH agonist post laparoscopic cystectomy for endometrioma has increased pregnancy rate than GnRH agonist alone, though not statistically significant.[54] Factors like age <35, AFC >7 and transfer of only two embryos are associated with positive outcomes in in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) cycles in women who have cystectomy for endometrioma.[55]

Various treatments for infertility in endometrioma were analysed by Alborzi *et al.*[56] In their meta-analysis, they compared four groups – surgery and ART; surgery and spontaneous pregnancy; aspiration/sclerotherapy and ART; and ART alone. Their results showed no significant differences among the four groups in clinical pregnancy rates. ART alone in infertile endometriotic women had the lowest pregnancy rate among them. The fertilisation rate was also similar among the four groups. Surgery and aspiration of the cyst pre-ART procedures improved the fertilisation rate without any change in the requirement of gonadotrophins or duration of stimulation in the ART cycle. Removal of an endometrioma may relieve pressure over ovarian tissue and reduce the inflammatory fluid of the cyst.

Retrieval of ovum from ovaries can be challenging due to the size and position of the endometrioma. Benaglia[57] observed that the occurrence of incomplete follicular aspiration was seen more frequently in patients with endometriomas (OR

3.6, 95% CI 1.4–9.6). Transfixation of cysts was done in 8 cases (14%). In 9 women there was accidental contamination of the follicular fluid with the endometrioma content (16%). No pelvic infections or cyst ruptures were recorded.

Pelvic inflammatory disease (PID) in patients with endometrioma patients often fails to respond to antibiotic treatment and requires a surgical approach.[58] For women with endometrioma, prophylactic antibiotics should be given at the time of ovum pickup, as there is minimal risk of abscess formation during follicle aspiration.

Maintenance hormone treatments can prevent the recurrence of endometrioma. Combined postoperative adjuvant therapy and maintenance treatment are better than GnRHa alone in preventing anatomical relapse.[59] Combined postoperative treatment with GnRHa-DNG is better than single therapy in decreasing recurrence. Other regimens like DNG and GnRHa-OCP are also effective.[60]

Risk factors for recurrence of endometrioma include age at surgery, size of the cyst, CA125 level, revised american society for reproductive medicine (rASRM) score, previous surgery for endometriosis, pre-operative medication, post-operative medication, associated adenomyosis, and dysmenorrhea. Pregnancy protects from recurrence post-surgery.

## CONCLUSION

Endometrioma is often found in young women. There is no consensus as to which treatment is better, hormonal or surgical. An individualised approach is advocated depending on the presenting complaints. For women desirous of pregnancy, evidence shows ART has benefits over cystectomy. Surgery can cause inadvertent loss of ovarian tissue and affect the ovarian function. Recurrence rate has to be kept in mind while treating such women.

### Author contributions

PS: Reviewing the literature and writing the manuscript.

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