

## Ovarian Endometrioma and Infertility

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**Abstract:** The core definition of endometriosis is when endometrial glands and stroma are identified outside the uterine cavity. It is estimated to affect 2-10% of women in their reproductive age, and 50% of patients complain of infertility. Ovarian endometrioma is a common yet a specific presentation of the disease. This review discusses the effect of ovarian endometrioma on fertility and its management.

**Keywords:** Ovarian endometrioma, Infertility, Ovarian cystectomy, IVF

### 1. INTRODUCTION

Ovarian endometrioma is defined as a cystic formation within the ovary lined by ectopic endometrium<sup>[1]</sup>. Its incidence is approximately 17% of subfertile women<sup>[2]</sup>. It is present in 17-44% of patients with endometriosis<sup>[3]</sup>, and it is estimated that 20-40% women undergoing assisted reproductive techniques (ART) have endometriosis<sup>[4]</sup>.

Three main theories exist for the formation of endometrioma. The first being invagination secondary to bleeding of a superficial implant. It may also be formed through invagination secondary to metaplasia of coelomic epithelium in cortical inclusion cysts, and finally endometriotic transformation of functional cysts.

The diagnosis of endometrioma is tricky as it may be asymptomatic, however it may present with dysmenorrhea, dyspareunia, infertility and sometimes adnexal mass<sup>[5]</sup>. The tumor marker CA-125 can be elevated in the presence of an endometrioma, but not accurate<sup>[6]</sup>. Newer marker, follistatin, is showing more promise but its value still remains controversial<sup>[7-9]</sup>.

Trans-vaginal ultrasound for the diagnosis of endometrioma has been reported to have a sensitivity range between 84-100%, and a specificity range between 90-100%<sup>[10-11]</sup>. Endometriomas can have a wide range of appearances on ultrasound, which may vary from an anechoic cyst to a solid appearing mass<sup>[5]</sup>.

Typically in more than 80% of cases, they appear as a thick walled ovarian cyst containing homogenous "ground-glass" content with no internal vascularity<sup>[5,12]</sup>. Endometriomata maybe unilateral or bilateral; uni- or multilocular, sometimes single or multiple, and usually more common on the left side<sup>[13]</sup>.

### 2. EFFECT OF OVARIAN ENDOMETRIOMA ON FERTILITY

Endometriosis itself causes infertility through<sup>[14,15]</sup>:

- Distortion of the pelvic anatomy.
- Abnormal utero-tubal transport.
- Altered peritoneal function.
- Altered humoral and cell mediated immunity.
- Impaired implantation.
- Abnormal oocyte and embryo quality.

A meta-analysis has shown that the pregnancy rate was significantly lower compared to women with tubal infertility<sup>[2]</sup>. This effect seems to be mediated through altered oocyte quality<sup>[16]</sup>. Pelvic endometriosis may affect oocyte quality perhaps through increased granulosa cell apoptosis<sup>[17]</sup>. Also cases with endometrioma have fewer oocytes retrieved during in-vitro fertilization (IVF)<sup>[2,18]</sup>.

Newer evidence is emerging that deep ovarian endometriosis alters the local environment through intra-ovarian oxidative damage<sup>[19]</sup>. Other studies have shown that the spontaneous ovulation rate is significantly lower in the affected ovary<sup>[20,21]</sup>. A dose-response effect was

observed; when only one endometrioma was present the ovulation rate in the affected ovary was 35%, but when an ovary contained two or more cysts, the ovulation rate was only 19%<sup>[22]</sup>.

An ovarian endometrioma tends to be a sentinel marker of more disseminated endometriosis<sup>[23]</sup>. The reality is that this condition is usually accompanied by other pelvic lesions and adhesions<sup>[24]</sup>. This combined effect leads to a more severe disease, which is associated with lower fertility rates<sup>[5]</sup>.

### 3. MANAGEMENT OF OVARIAN ENDOMETRIOMA

Is surgery always the answer when ovarian endometriomas are diagnosed with ultrasound? This Depends on a variety of factors which include: age, parity, duration of infertility, associated pain, affordability of treatment, and previous ovarian surgery<sup>[25]</sup>.

#### 3.1. Expectant Management

The scan is repeated in in 2-3 months to exclude a functional cyst or a hemorrhagic corpus luteum cyst. These conditions will resolve with time, and given that endometriomas have an average growth rate of approximately 0.5 cm per 6 months, the size of the endometrioma will not be significantly affected<sup>[26]</sup>.

#### 3.2. Medical Treatment

Gonadotropin releasing hormone (GnRH) agonists or danazol shrinks the size of endometriomas 50%<sup>[5,27]</sup>. A Meta-analysis had shown a fourfold increase in the odds of clinical pregnancy when GnRH agonists were used 3–6 months as pretreatment to IVF in women with endometriosis<sup>[28]</sup>.

Other authors compared pre-surgical medical therapy versus surgery alone<sup>[29]</sup>, ovulation suppression versus placebo<sup>[30]</sup>, and a meta-analysis which included three reviews comparing GnRH agonists versus antagonists<sup>[31]</sup>. In all cases there was no evidence of a significant difference in effectiveness, and the quality of the evidence was either low or very low.

#### 3.3. Controlled Ovarian Stimulation and Intrauterine Insemination

In 15,000 studied COH-IUI cycles, endometriosis to be an unfavorable predictor of pregnancy<sup>[32]</sup>. One IVF cycle was found to be more effective than six cycles of COH-IUI<sup>[33]</sup>. This may be related to more significantly altered tubo-ovarian anatomy<sup>[14,34]</sup>.

### 3.4. Surgical Intervention

Usually a conservative approach is the best management, however sometimes surgical interference may be needed in the form of aspiration, ablation or cystectomy.

#### 3.4.1. Aspiration

The rationale behind it is that the endometriotic lining becomes compressed and atrophic. So aspiration will resolve the condition<sup>[3]</sup>. Its advantages include being simple, minimally invasive procedure, and cystectomy for cysts >3 cm carries an increased risk of diminished ovarian reserve after surgery<sup>[35]</sup>.

Its effect on IVF is controversial as both Dicker et al<sup>[36]</sup> and Suganuma et al<sup>[37]</sup> reported better and worse outcomes respectively. However it's not without risk as surgical intervention, pelvic abscess, and a recurrence rates 83.3% has been reported<sup>[35,38-40]</sup>.

#### 3.4.2. Chemoablation

In chemoablation the process of sclerotherapy destroys the epithelial lining of the cyst and hereby reduces the recurrence<sup>[41,42]</sup>.

Various sclerosing agents have been tried, including 95% ethanol, methotrexate, tetracycline, and IL-2<sup>[43-45]</sup>.

The recurrence rate for sclerotherapy varies between 9.1% and 66.7%. There are not enough studies to conclude its further impact on fertility<sup>[42]</sup>, and there is an increased risk of associated pelvic abscess<sup>[46]</sup>.

#### 3.4.3. Cystectomy

Whether the approach for the cystectomy was laparotomy or laparoscopic, the procedure carries potential difficulties and complications. Cystectomy often leads to bleeding of the vascular bed in the hilus, which requires meticulous hemostatic control<sup>[47]</sup>.

Many studies showed that after excision there was an increased risk of diminished ovarian reserve<sup>[47,48]</sup>.

#### ➤ Excision versus Ablation

In excision of the endometrioma, the cyst wall is incised either with or without the use of electro-surgical or laser energy. Then a combination of scissors (or a monopolar hook) and grasping forceps is used to excise or 'strip away' the cyst wall from the underlying cortex.

Ablation on the other hand involves first opening and then draining the endometrioma, or

making a window in the wall of the cyst (fenestration), the cyst wall is then destroyed by either electro coagulation, or some form of laser energy is used<sup>[49,50]</sup>.

A Cochrane Review suggested a benefit of excisional surgery over drainage or ablation for achieving spontaneous pregnancy<sup>[51,52]</sup>. Another one found no evidence of a difference between surgery (aspiration or cystectomy) and expectant management in clinical pregnancy rates prior to ART<sup>[31,51]</sup>.

### ➤ Hemostasis: Bipolar Electro Coagulation, Harmonic Scalpel or Suturing?

Electro coagulation was associated with a reduction in ovarian reserve<sup>[53,54]</sup>. A Meta-analysis showed that Suturing for hemostasis was associated with a more favorable outcome for ovarian reserve than bipolar electro-coagulation<sup>[55]</sup>. Another study showed that suturing may also reduce postoperative adhesions compared with bipolar surgery<sup>[56]</sup>.

Studies using topical hemostatic agent (gelatine-thrombin matrix) showed good control of minor bleeding at the end of laparoscopic stripping<sup>[57,58]</sup>.

### ➤ To Remove or not to Remove?

This controversial question plagues the minds of gynecologists. A Cochrane review suggested that excision of endometrioma >3 cm led to five fold spontaneous pregnancy rate<sup>[52]</sup>.

Other meta-analysis and ESHRE Guidelines concluded that there is no significant effect on ovarian response to stimulation and IVF pregnancy rates compared with no treatment<sup>[4,31,59]</sup>.

### ➤ Pre-and Post-Surgical Interventions

No evidence to support the use of either Pre- or post-surgical medical therapy (Danazol, GnRH $\alpha$ , progestogens, gestrinone, OCPs) for increasing pregnancy rates<sup>[29,51,60]</sup>.

### ➤ Recurrences Following Surgery

Recurrences are less after excision than ablation<sup>[52,61]</sup>. Recurrence decreases with increasing age<sup>[62,63]</sup>. Two out of the three RCTs recommended postoperative use of cyclic OCPs to delay recurrence<sup>[64-66]</sup>.

## 3.5. In-Vitro fertilization (IVF)

There are pathophysiological effects on ovary which include a need for increased cumulative

doses of FSH medication and the production of fewer follicles following stimulation<sup>[5]</sup>.

During ovum pick up, the puncture by the needle may increase the associated risk of pelvic abscess. The ovaries are often adherent to the posterior surface of the uterus, where they may be out of reach. The bowel loops may also be fixed in the path of the aspiration needle<sup>[67,68]</sup>.

Endometriosis affects oocyte number but not embryo quality or pregnancy rates and outcome, whether or not an endometrioma is present<sup>[18]</sup>. Endometrioma has adverse effects only on follicle number and oocytes quality<sup>[69]</sup>. Yang et al<sup>[70]</sup> showed same results but less total number of embryos and M2 oocytes. Only a single study showed lower embryo quality and implantation rates, in the presence of endometrioma, however pregnancy outcome was also unaffected<sup>[71]</sup>. Other studies also showed no adverse effect on IVF outcome<sup>[14,67,68]</sup>. Fernando et al reported that endometriomas increase the rate of preterm birth<sup>[72]</sup>.

Meta-analysis studying medical Interventions prior to IVF comparing GnRH agonist to GnRH antagonist showed that there was improved ovarian response to stimulation, and the number of oocytes retrieved. However there was no difference in clinical pregnancy rates between either protocol<sup>[31,51]</sup>. Only a meta-analysis by Sallam et al reported more pregnancies with ultra-long GnRH agonist down-regulation, however it only included three trials and there was a lot of heterogeneity in the inclusion criteria of the included studies<sup>[28]</sup>.

Meta-analysis studying surgical interventions prior to IVF have shown that there is no benefit of laparoscopic aspiration, cystectomy, or transvaginal aspiration of endometrioma over expectant management regarding the clinical pregnancy rate<sup>[31]</sup>.

## 4. CONCLUSION

Traditional treatments modalities such as cystectomy and ablation increase the rate of spontaneous pregnancy and lower incidence of recurrence after removal. However there is no improvement in IVF outcomes and they can potentially cause damage to the ovarian reserve. Less invasive newer and combined techniques are being developed that reduce the damage to the ovarian reserve after cystectomy. More research is needed to determine how these procedures affect IVF outcomes.

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