The Effect of Surgery for Endometriomas on Fertility

1. Background

Endometriosis is an inflammatory condition characterised by the presence of tissue resembling endometrium in sites other than the uterine cavity.\(^1\) It is estimated that 5–10% of women, mainly of reproductive age, are affected by the condition, with a reported higher prevalence in subgroups, such as those affected by infertility. Ovarian endometrioma(s) can be found in up to 17–44% of women with endometriosis and are often associated with the severe form of the disease.\(^2,3\) Whilst the pathognomonic mechanisms of endometriosis per se remain elusive, it is widely believed that most endometriotic lesions develop from retrograde menstruation. Endometriotic ovarian cysts (known as ‘endometriomas’) are mostly thought to occur through invagination of endometriotic tissue/cells through the ovarian serosa, for example, during remodelling of the ovarian cortex after ovulation.

The presence of endometriomas often presents a clinical dilemma during the course of fertility treatment. For example, there can be uncertainty regarding the decision on whether to operate and balancing the potential detrimental effect of surgery on the ovarian reserve against the potential benefit that may be gained.

Current guidelines often rely on the evidence from either small and/or retrospective controlled studies. In particular, for assisted reproductive treatment (ART) some of the studies were conducted in the 1980s and 1990s. Since then, IVF success rates have significantly improved due to changes in stimulation protocols and available drugs, as well as the introduction of laboratory techniques such as intracytoplasmic sperm injection and blastocyst cultures.

This Scientific Impact Paper will review the evidence of endometrioma-associated infertility and, in particular, the effect of surgery.

2. Endometriomas and subfertility

Fecundity rates may be reduced in women with endometriosis, potentially related to the severity of the disease (revised American Society for Reproductive Medicine [rASRM] classification).\(^4\) Of women with a surgical diagnosis of endometriosis, 30–50% are subfertile, of which, 50% with mild endometriosis will conceive without intervention over a period of up to 2 years, in contrast to 25% with moderate endometriosis and fewer still with severe disease.\(^5,6\) The presence of ovarian endometriomas is usually associated with rASRM staging of moderate or severe disease.\(^2\) A number of theories for endometriosis-related infertility have been proposed, including chronic inflammation, tuboperitoneal anatomic distortion and reduced endometrial receptivity, leading to compromised oocyte and embryo quality, and ovarian reserve, but the precise mechanism has yet to be determined.\(^7\)

3. Potential mechanisms for endometrioma – associated infertility

Chronic inflammation

Endometriosis is associated with dysregulation of the immune system.\(^7\) Peritoneal fluid from women with endometriosis has been found to contain increased numbers of immune cells, including
macrophages, and mast, natural killer and T cells, as well as elevated levels of growth factors, chemokines and cytokines. The enhanced inflammatory state can affect the quality of the oocytes and impair ovarian function, resulting in defective folliculogenesis and fertilisation, findings similar to those attributed to endometriomas. As endometriomas and peritoneal disease often occur concomitantly and might be pathogenically linked, it is difficult to establish whether inflammation affects fertility for both clinical presentations of endometriosis.

**Oocyte and embryo quality**

Altered aromatase enzyme activity with impaired intrafollicular estrogen concentrations may result in an impaired fertilisation capacity of the oocytes. Embryo quality is also reduced in the presence of endometriosis, as suggested by their slower development compared with embryos derived from women with tubal disease.

**Ovarian reserve**

The presence of ovarian endometriomas, especially if bilateral, can affect the ovarian reserve, which impacts on the ovarian response to gonadotrophins during ART. Histological studies have reported a significant reduction in the primordial follicle cohort in affected ovaries. Follicle depletion may be secondary to damage induced by the endometriosis-associated inflammatory reaction and by increased tissue oxidative stress leading to fibrosis. A group of potentially toxic agents, such as free iron, that can diffuse through the cyst wall of the endometrioma, as well as long-lasting mechanical stretching of ovarian cortex, can all have a detrimental impact on the ovarian reserve. Most important, however, is the negative effect of ovarian surgery, especially if repeated, on ovarian reserve (see below).

**4. Management options**

While the options include expectant, medical and surgical management, the recommended treatment is guided by the symptoms of the patient and other fertility prognostic factors, including age, associated symptoms and ovarian reserve. Treatment of incidental disease in otherwise asymptomatic women is currently not recommended, since the development of endometrioma(s) and its progression is not well understood.

**4.1 Spontaneous conception**

**4.1.1 Conservative management for spontaneous conception**

Young women with regular menstrual cycles and an incidental finding of an ovarian endometrioma without suspicion of malignancy who wish to conceive should be encouraged to try natural conception before seeking fertility treatment. While the evidence of the impact of an endometrioma on spontaneous conception is limited, a prospective study (n = 244) reported a 43% spontaneous pregnancy rate in the presence of unilateral endometrioma of varying sizes (diameter of 5.3 ± 1.7 cm [mean ± SD]). The study also reported similar ovulation rates in the affected ovary to the healthy ovary (49.7% versus 50.3%), not influenced by the laterality of the endometrioma(s), its number and size, or by the presence of deep endometriosis diagnosed by ultrasound. This finding contradicted previously reported data in a smaller prospective study (n = 70), of reduced ovulation in the affected ovary (31% versus 69%). For women with a naturally or abnormally reduced ovarian reserve, conservative management for fertility should be weighed against the potential benefits of surgery or fertility treatment.
4.1.2 Medical treatment for spontaneous conception

Medical treatment ranges from simple analgesia to hormonal manipulation. Hormone treatments (oral contraceptive pill, progestins and gonadotropin analogues) are aimed at reducing endogenous estrogen concentrations and the estrogen effect on endometriotic tissue. However, they should not be prescribed in women wishing to conceive since they do not improve spontaneous pregnancy rates.

4.1.3 Surgical treatment for spontaneous conception

There is controversy regarding the surgical management of endometriomas in women undergoing treatment for infertility. While surgical treatment may improve spontaneous pregnancy rates by restoring the pelvic anatomy, it remains unclear as to whether surgical intervention on the ovary itself is beneficial. However, surgical treatment cannot reverse the inflammatory and biomolecular changes shown to influence fertilisation and implantation. Furthermore, there are concerns about safety of surgical treatments, with a reported reduction in the ovarian reserve\textsuperscript{19,20} and the small added risk of an oophorectomy. In contrast, concerns have been raised about the effect of an endometrioma on oocyte quantity and quality. This conflict suggests that management should be individualised and based upon clinical factors, including pain symptoms, size of the cyst(s) and concerns over potential malignancy.

When performing surgery, ovarian endometriomas are best managed by performing a cystectomy as opposed to drainage and coagulation, with an overall lower recurrence risk and higher spontaneous postoperative pregnancy rate, particularly if the cyst is more than or equal to 3 cm in diameter. Hart et al.\textsuperscript{21} summarised two randomised controlled trials (RCTs) which showed a beneficial effect of excisional surgery over drainage or ablation of an endometrioma in achieving a spontaneous pregnancy in subfertile women (OR 5.24, 95% CI 1.92–14.27; 88 participants; 2 trials). However, this can lead to a significant reduction in the number of follicles, especially in women who have undergone previous ovarian surgery, and therefore, ovarian reserve, reflected by a sustained decrease in anti-Müllerian hormone (AMH) levels.

4.2 Assisted reproductive technology

4.2.1 Intrauterine insemination (IUI)

An RCT has shown that IUI combined with controlled ovarian stimulation increases the live birth rate (OR 5.6, 95% CI 1.18–17.4) in couples with minimal to mild endometriosis compared with expectant management,\textsuperscript{22,23} but no studies have examined the effect of IUI in women with endometrioma(s), or moderate or severe endometriosis, often associated with endometriomas, which can be attributed to the retrospective nature of the ASRM scoring system. However, moderate to severe disease more frequently includes cases with impaired tubal function, which would suggest higher success rates with in vitro fertilisation (IVF) than with IUI.

4.2.2 IVF

IVF is an effective treatment to increase the chances of conception, especially in the presence of anatomical distortion secondary to moderate to severe disease.\textsuperscript{24} However, it remains controversial as to how IVF success rates are affected by the presence of an endometrioma.

Effect of endometriomas on IVF outcome
Evidence of impact of an endometrioma on ovarian response during IVF is equivocal. Systematic reviews of controlled studies have reported similar ovarian responses in women with endometriosis to controls with no evidence of endometriosis, and in women with a unilateral ovarian endometrioma compared to contralateral normal ovaries. While most studies included in the latter systematic review evaluated women with small endometrioma(s), two studies reported on the potential detrimental effect of the size of the endometrioma on ovarian response especially when this was equal to or more than 3 cm in diameter. In one systematic review, ovarian response was lower with a lower number of oocytes retrieved (mean difference –0.23; 95% CI 0.37–0.1) and a higher cancellation rate (OR 2.83; 95% CI 1.32–6.06) in women with an endometrioma, although the total stimulation dose of gonadotrophins used was comparable. However, live birth (OR 0.98; 95% CI 0.71–1.36), pregnancy (OR 1.17; 95% CI 0.87–1.58) and miscarriage rates (OR 1.7; 95% CI 0.86–3.35) following IVF were similar in women with an endometrioma compared to women with no endometriosis. When compared to women with peritoneal endometriosis in the absence of an endometrioma, IVF outcomes (live birth, pregnancy, miscarriage and cycle cancellation rates, and mean number of oocytes retrieved) were similar in women with an endometrioma. No data on adverse events, such as bleeding, infection or pain, were reported in these studies.

Basal follicle stimulating hormone levels were higher in women with an endometrioma compared with women with no evidence of endometriosis (three studies; n = 491), however, the antral follicle count was similar between the two groups (two studies; n = 433). Although equivocal, most studies report that the observed reduced ovarian response, especially in the presence of larger endometriomas, is related to an overall reduced ovarian reserve in women with an endometrioma.

In contrast, an adverse impact of endometrioma(s) and endometriosis on oocyte quality has been suggested by Simón et al., who reported on data from an oocyte donation programme, in which women with endometriosis were shown to have the same chances of implantation and pregnancy as other oocyte recipients, when the oocytes came from donors without known endometriosis. However, the implantation rates were reduced in healthy recipients when the oocytes came from donors with endometriosis, suggesting a negative effect of the condition on oocyte quality.

Nevertheless, as reviewed by the European Society of Human Reproduction and Embryology (ESHRE) guidelines for the management of endometriosis, no such differences have been demonstrated in very large databases including more recent IVF cycles, such as the Human Fertilisation and Embryology Authority of the Society for Assisted Reproductive Technology.

**Surgical treatment before IVF**

Surgical treatment of endometrioma(s) prior to IVF is widely practiced, although debatable on its effect and need. A systematic review (five controlled studies; n = 655), reported similar live birth (OR 0.9; 95% CI 0.63–1.28), clinical pregnancy (OR 0.97; 95% CI 0.78–1.2) and miscarriage rates (OR 1.32; 95% CI 0.66–2.65) following IVF treatment in women with surgically treated endometriomas compared to those with intact endometriomas. While the number of oocytes retrieved and the cancellation rates were comparable, women with a surgically treated endometrioma had a lower antral follicle count and required higher doses of gonadotrophins for ovarian stimulation. Interestingly, women who had undergone surgical management for a unilateral endometrioma had a lower number of oocytes retrieved from the surgically treated ovary (mean difference –2.59; 95% CI –4.13 to –1.05) when compared with the contralateral normal ovary, indicating a reduction in the ovarian reserve following surgical intervention, as has been reported in several other studies. The potential physiological compensation by the normal ovary for the compromised ovary, in conjunction with the higher follicle stimulating hormone doses required for ovarian stimulation, may account for the similar IVF outcomes noted in women whom have undergone surgical treatments for their endometrioma(s).
A Cochrane review incorporating two small RCTs has reported similar pregnancy rates between surgery (cystectomy or aspiration) and expectant management. While no differences in pregnancy rates have been shown between a cystectomy and aspiration of an endometrioma, a cystectomy is associated with a lower ovarian response following controlled stimulation, with a lower number of mature oocytes retrieved, raising concern on the potential adverse influence of a cystectomy on the ovarian reserve. In contrast, another meta-analysis incorporating three controlled studies (including non-RCT studies) reported similar ovarian responses and pregnancy rates following IVF in women with an endometrioma surgically managed with a cystectomy versus transvaginal aspiration prior to IVF treatment. Based on the available evidence, the ESHRE guideline concludes that a cystectomy for an endometrioma larger than 3 cm, prior to undergoing IVF treatment, does not improve pregnancy rates. However, surgery prior to ART can be considered for the management of endometriosis-associated pain or for increasing the accessibility of the follicles during oocyte retrieval procedures.

Despite the lack of evidence of the clear benefit of surgical treatment for the management of an endometrioma on pregnancy rates, conservative management in women with an endometrioma undergoing IVF treatment has been questioned, in addition to the various potential drawbacks and risks. The presence of an endometrioma may theoretically interfere with ovarian responsiveness to controlled stimulation and oocyte competence, as well as pose potential risk and technical difficulties during oocyte retrieval, including the associated risks to injury to adjacent organs due to altered pelvic anatomy with the presence of adhesions, infection and abscess formation, follicular fluid contamination with endometrioma content, progression of endometriosis, further growth and rupture of the endometrioma, missed occult malignancy and cancer development in later life. A systematic review has evaluated these potential risks, concluding there is a lack of evidence on risks of reduced ovarian responsiveness and reduced oocyte competence. In contrast, surgery for an endometrioma may potentially reduce ovarian reserve as evidenced by a decrease in the anti-Müllerian hormone levels and reduced responsiveness to gonadotrophin stimulation. While the risk of technical difficulties during oocyte retrieval is low based on very limited reports, there are no data to suggest that surgery for an endometrioma has not been proven to prevent adhesion reformation and facilitate oocyte retrieval effectively. While the available data exclude a clinically relevant effect of IVF on progression of pelvic endometriosis and ovarian endometriomas, the risks of infection from an endometrioma and follicular fluid contamination are very small, and unable to justify surgery for the presence of an endometrioma prior to treatment through IVF. The risk of missing an occult malignancy in an endometrioma is extremely low and in the absence of any nonreassuring ultrasonographic features, surgery is not warranted. Although rare, the risk of the potential for the development of ovarian cancer later in life can be a serious concern, with the lifetime probability increasing from 1% to 2% in the presence of an endometrioma. However, in the context of IVF treatment, delaying surgery for a few months or years, until the IVF processes have been completed or following delivery, is unlikely to expose the women to a significantly increased risk of cancer.

The ESHRE guideline discusses the importance of women being appropriately counselled about the risk of reduced ovarian function following surgical intervention and even the possible risk of an oophorectomy. The decision to proceed with surgery for an endometrioma should be carefully considered, including the various prognostic factors that can influence the success of an ART cycle, such as the age of the woman, ovarian reserve status, unilaterality or bilaterality of the disease, number and size of the cysts, symptoms, presence or absence of suspicious ultrasonographic features and history of previous ovarian surgery. Asymptomatic women, 38 years of age or above, with a reduced ovarian reserve, bilateral endometriomas or a history of prior ovarian surgery may benefit from proceeding directly with IVF treatment, since surgery may further compromise ovarian function and delay the start of treatment. Surgery may be considered first line in highly symptomatic conditions.
women, those with an intact ovarian reserve, unilateral and large cysts, or with suspicious ultrasonographic features.

5. Opinion

- Endometriomas are associated with reduced monthly fecundity rates, although a direct causal relationship has not been well established.
- Repeated or extensive ovarian surgery has a detrimental impact on ovarian reserve and this should be considered when deciding whether or not to operate. The theoretical benefit of performing surgery to improve pelvic anatomy and accessibility is plausible, but has not been supported with scientific evidence.
- Until robust evidence from large RCTs incorporating modern treatment modalities are available, many uncertainties will remain on the optimal treatment of an endometrioma. In the interim, management decisions should be based on individual circumstances, such as patient choice, age, ovarian reserve and associated symptoms.

References


Appendix I: Risks and benefits of expectant and surgical management of an endometrioma

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<thead>
<tr>
<th>Expectant management</th>
<th>Surgical management</th>
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<tr>
<td><strong>Potential benefits:</strong></td>
<td><strong>Potential benefits:</strong></td>
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<tr>
<td>• Avoids surgery and its associated complications</td>
<td>• Alleviates symptoms</td>
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<tr>
<td>• No further compromise on ovarian reserve</td>
<td>• Histological confirmation of diagnosis (excludes malignancy)</td>
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<td></td>
<td>• Reduced risk of cyst complications</td>
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<td></td>
<td>• Facilitates ovarian access</td>
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<tr>
<td><strong>Potential risks:</strong></td>
<td><strong>Potential risks:</strong></td>
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<tr>
<td>• Symptoms (pain)</td>
<td>• Surgical risks</td>
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<tr>
<td>• Cyst rupture</td>
<td>• Reduced ovarian reserve</td>
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<tr>
<td>• Difficult ovarian access during oocyte retrieval procedures</td>
<td>• Postoperative adhesions</td>
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<tr>
<td>• Infection of an endometrioma</td>
<td>• Potential delay of assisted reproductive treatment</td>
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<td>• Follicular fluid contamination</td>
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<td>• No histological diagnosis</td>
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<td>• Accelerated progression of the disease</td>
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