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The Effect of Surgery for Endometriomas on Fertility

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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 6–10% of women,[1] mainly of reproductive age, are affected by the condition, with a reported higher prevalence in certain 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] While the pathognomonic mechanisms of endometriosis per se remain elusive, it is widely believed that most endometriotic lesions develop from retrograde menstruation and are possibly associated with immune dysfunction, which can interfere with endometrial implant clearance.[1] 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.[4]

The presence of an endometrioma can often present a clinical dilemma during the course of fertility treatment. For example, there can be uncertainty regarding the decision to operate or to manage conservatively, 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 referenced studies were conducted in the 1980s and 1990s. Since then, in vitro fertilisation (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 culture.

This Scientific Impact Paper will review the current evidence for management of endometriomas within the context of infertility treatment.

2. Endometriomas and infertility

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).[5] 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.[6]

3. Potential mechanisms for endometrioma-associated infertility

3.1 Chronic inflammation

Endometriosis is associated with dysregulation of the immune system.[6] 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.[7–9] The enhanced inflammatory state can affect the quality of the oocytes and impair ovarian function, resulting in defective folliculogenesis and fertilisation.[10] As endometriomas and peritoneal disease often occur concomitantly and might be pathogenically linked, it is difficult to establish which of these inflammatory clinical presentations of endometriosis affects fertility.

3.2 Oocyte and embryo quality

Endometriomas and associated pelvic endometriosis may affect oocyte and embryo quality adversely. While embryo development in women with endometriosis is slower compared to women with tubal disease,[11] women with moderate-to-severe disease receiving eggs from a donor without endometriosis have been shown to have similar pregnancy rates to other egg recipients.[12] An altered follicular environment, represented by elevated concentrations of progesterone and interleukin-6 and decreased concentration of vascular endothelial growth factor, may be responsible for alterations within the oocyte, leading to impaired fertilisation capacity of the oocytes and reduced embryo quality with low implantation potential.[13]

3.3 Ovarian reserve

The presence of ovarian endometriomas, especially if bilateral, can affect the ovarian reserve, impacting the ovarian response to gonadotrophins during ART. A histological study[14] 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.[15] 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.[16] Most importantly, however, is the negative effect of ovarian surgery on ovarian reserve, especially if performed repeatedly (see sections 4.1.2, 4.1.3 and 4.1.4).

4. Management options

While the options include expectant and surgical management, the recommended treatment should be guided by: the woman's symptoms; fertility prognostic factors, including age and ovarian reserve; previous treatment history with specific reference to past surgical interventions; nature of the cyst; and the wishes of the woman.[17] Treatment of incidental disease in otherwise asymptomatic women is currently not recommended, as the development and natural progression of endometriomas 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.[15] While the evidence of the impact of an endometrioma on spontaneous conception is limited, a prospective observational study[18] (n = 244) reported a 43% spontaneous pregnancy rate during the 6-month follow-up period in the presence of unilateral endometriomas of varying sizes (diameter 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 endometriomas, their 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),[19] 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 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 as it may not reverse the inflammatory and biomolecular changes shown to influence fertilisation and implantation.[20] Furthermore, there are concerns regarding the safety of surgical treatments, with a reported reduction in the ovarian reserve[21,22] and the small added risk of requiring 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 cysts and concerns over potential malignancy. Consideration should be given to surgical treatment being undertaken by a gynaecologist with specific expertise in endometriosis and fertility, in order to minimise the impact on the ovarian reserve and provide a holistic assessment regarding future fertility management.

When performing surgery, ovarian endometriomas are best managed by performing a cystectomy, as opposed to drainage and coagulation, which is associated with an overall lower recurrence risk and higher spontaneous postoperative pregnancy rate, particularly if the cyst is 3 cm or more in diameter. Hart et al.[23] 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; n = 88; two trials). However, this can lead to a significant reduction in the number of ovarian 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. While data from observational controlled studies[24,25] investigating ovarian endometrioma drainage and ablation using energy with minimal thermal spread, such as CO_2 laser or plasma energy, indicated good results; in terms of a satisfactory fertility outcome, reduced ovarian damage and reduced recurrence risks, RCTs are needed to be able to draw definitive conclusions.

4.1.3 Effect of endometriomas on IVF outcome

Evidence of the 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,[26] and in women with a unilateral ovarian endometrioma compared to contralateral normal ovaries.[27] While most studies included in the latter systematic review evaluated women with small endometriomas, two studies[28–30] reported on the potential detrimental effect of the size of the endometrioma on ovarian response especially when this was 3 cm or more in diameter. In one systematic review,[31] 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 dosage of gonadotrophin 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.[32] 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[33,34] 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 endometriomas and endometriosis on oocyte quality has been suggested by Simón et al.,[35] who reported on data from an oocyte donation programme in which women with endometriosis were shown to have the same chance 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 the condition had a negative effect on oocyte quality. Nevertheless, as reviewed by the European Society of Human Reproduction and Embryology (ESHRE) guideline for the management of endometriosis,[17] no such differences have been demonstrated in large databases that include more recent IVF cycles, such as the Human Fertilisation and Embryology Authority and the Society for Assisted Reproductive Technology.

4.1.4 Surgical treatment prior to IVF

Surgical treatment of endometriomas prior to IVF is widely practised,[36] although debatable on its effect and need. A systematic review[32] (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.[22,31,37] 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 who have undergone surgical treatments for their endometriomas.[32]

A Cochrane review[38] incorporating two small RCTs has reported similar pregnancy rates for surgical (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 about the potential adverse influence of a cystectomy on ovarian reserve. In contrast, a meta-analysis[32] 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 compared to transvaginal aspiration prior to IVF treatment. Based on the available evidence, the ESHRE guideline group[17] concluded 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, for increasing the accessibility of the follicles during oocyte retrieval procedures, or to ameliorate any concern for malignancy.

Despite the lack of evidence of the clear benefit of surgical treatment for the management of an endometrioma on pregnancy rates, and the various potential drawbacks and risks, conservative management in women with an endometrioma undergoing IVF treatment has been questioned. 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[27] evaluating the potential risks of conservative management in women with a known endometrioma undergoing IVF concluded that there was insufficient evidence on the risks of reduced ovarian responsiveness and reduced oocyte competence. Furthermore, surgery for an endometrioma may potentially reduce ovarian reserve, as evidenced by a decrease in the AMH levels[22] and subsequent responsiveness to gonadotrophin stimulation.[39]

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 will 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 (0–1.9%) and follicular fluid contamination (2.8–6.1%) are very small, and unable to justify surgery for the presence of an endometrioma prior to IVF treatment.

The risk of missing an occult malignancy in an endometrioma is extremely low and in the absence of any suspicious radiological features, surgery is not warranted. Although rare, the risk of developing 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.[40] However, in the context of IVF treatment, delaying surgery for a few months or years, until the treatment has been completed or following delivery, would usually be a reasonable course of action unless there are other immediate concerns.

The ESHRE guideline group[17] discussed 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 radiological features, extent of extraovarian disease and history of previous ovarian surgery.[41] Asymptomatic women, women of advanced reproductive age, those with reduced ovarian reserve, bilateral endometriomas or a history of prior ovarian surgery may benefit from proceeding directly with IVF, as surgery may further compromise ovarian function and delay the start of treatment. Surgery may be considered first line in highly symptomatic women, those with an intact ovarian reserve, unilateral and large cysts, and should be considered for cysts with suspicious radiological and clinical features. Endometriomas may be associated with extraovarian disease, including intestinal disease and deeply infiltrating endometriosis. Reproductive outcomes have not been shown to be improved by the excision of deeply infiltrating endometriosis, with surgical excision of endometriotic nodules providing symptomatic

benefit albeit potentially exposing the woman to significant surgical risks, to which the women should be appropriately counselled.[17]

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 on treatment and specifically, further surgery. The theoretical benefit of performing surgery to improve pelvic anatomy and accessibility is plausible, but has not been supported with substantive scientific evidence.
- Until robust evidence from large RCTs incorporating modern treatment modalities is available, many uncertainties will remain on the optimal treatment of an endometrioma. Meanwhile, management decisions should be based on individual circumstances, such as patient choice, age, ovarian reserve and associated symptoms.

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Appendix I: Risks and benefits of expectant and surgical management of an endometrioma for women undergoing assisted reproductive treatment (ART)

	Expectant management	Surgical management
Potential benefits	• Avoids surgery and its associated complications • No further compromise on ovarian reserve • Avoids delay in commencing ART	• Alleviates symptoms • Histological confirmation of diagnosis (excludes malignancy) • Reduced risk of cyst complications • Facilitates ovarian access
Potential risks	• Symptoms (pain) • Cyst rupture • Difficult ovarian access during oocyte retrieval procedures • Infection of an endometrioma • Follicular fluid contamination • No histological diagnosis • Accelerated progression of the disease	• Surgical risks • Reduced ovarian reserve • Postoperative adhesions • Potential delay of ART

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