Original Article

Endometriosis and Infertility – a consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence)

Juliette KOCH,[1] Katrina ROWAN,[2] Luk ROMBAUTS,[3] Anusch YAZDANI,[4] Michael CHAPMAN[5] and Neil JOHNSON[6]

[1]*IVF Australia, Bondi Junction, New South Wales, Australia,* [2]*Genea, Sydney, New South Wales, Australia,* [3]*Department of O&G, Monash University, Clayton, Victoria, Australia,* [4]*QFG Research Foundation, University of Queensland, St Lucia, Queensland, Australia,* [5]*Department of O&G, University of New South Wales, Randwick, New South Wales, Australia, and* [6]*University of Auckland, Auckland, New Zealand*

Endometriosis is common in women with infertility but its management is controversial and varied. This article summarises the consensus developed by a group of Australasian subspecialists in reproductive endocrinology and infertility (the Australasian CREI Consensus Expert Panel on Trial evidence group) on the evidence concerning the management of endometriosis in infertility. Endometriosis impairs fertility by causing a local inflammatory state, inducing progesterone resistance, impairing oocyte release and reducing sperm and embryo transport. Medical treatments have a limited role, whereas surgical and assisted reproductive treatments improve pregnancy rates. The role of surgery for deep infiltrative endometriosis and repeat surgery requires further evaluation and there is insufficient evidence for the use of anti-adhesives to improve fertility. Intrauterine insemination (IUI) and *in vitro* fertilisation (IVF) improve pregnancy rates but women with endometriosis have lower pregnancy rates than those with other causes of infertility. The decision about whether to operate or pursue assisted reproduction will depend on a variety of factors such as the patient's symptoms, the presence of complex masses on ultrasound, ovarian reserve and ovarian access for IVF, risk of surgery and cost. Some women with infertility and endometriosis may benefit from a combination of assisted reproduction and surgery.

Key words: assisted reproductive technology, endometriosis, *in vitro* fertilisation, infertility, surgery.

Introduction

Endometriosis is defined as the presence of endometrial glands or stroma outside the uterus and is diagnosed most commonly in women of child-bearing age. There is an increased prevalence of endometriosis in women with subfertility (up to 50%) compared to women with proven fertility (5–10%)[1] and a reduced monthly fecundity rate in women with endometriosis (2–10%) compared with fertile couples (15–20%).[2] A large multicentre prospective study in the 1990s showed a reduced fecundity in women with minimal endometriosis, but it was not statistically significant when compared to women with unexplained infertility.[3] However, among women undergoing donor insemination, there is increasing evidence that women with minimal and mild endometriosis have approximately half the chance of success of women without endometriosis.[4,5] Additionally, the fecundity in the control groups of women with endometriosis attempting to become pregnant naturally was approximately half that of a group with pure unexplained infertility without endometriosis.[6] Although there is substantial evidence for the relationship between endometriosis and infertility, a causal relationship has not yet been established.

The mechanisms for endometriosis related infertility are not fully understood and may be different for different stages of disease. In mild or minimal endometriosis, particularly where the fallopian tubes and ovaries are completely normal, mechanisms underlying reproductive failure are subtle and remain controversial. Studies demonstrate that endometriotic implants secrete oestradiol and progesterone which attracts macrophages, vascular endothelial growth factor (VEGF) and interleukin-8, and the lesions themselves also secrete pro-inflammatory cytokines (interleukin-1β, interleukin-8, interleukin-6 and

Correspondence: Dr Juliette Koch, IVF Australia, Suite 1601 Level 16, Westfield Tower 2, 101 Grafton St, Bondi Junction 2022, NSW, Australia. Email: drjuliettekoch@gmail.com

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tumour necrosis factor α).[7,8] It is this inflammatory state which is thought to impair fertility by having a toxic effect on gametes, embryos and impairing tubal motility.

Women with endometriosis have been found to have a deranged follicular environment high in cytokines IL-6 and TNF-alpha[9] and granulosa cells have increased rates of apoptosis.[10,11] Peritoneal macrophages from women with endometriosis have an enhanced ability to phagocytose sperm[12] and studies have shown a reduction in fertilisation rates in women with endometriosis undergoing assisted reproductive technology (ART).[13–17]

In addition, implantation may be impaired owing to the local inflammatory state and there is increasing evidence for defective eutopic endometrial receptivity.[18] Eutopic endometrium of women with endometriosis has been found to have an increased formation of antibodies to endometrial antigens, resistance to progesterone and decreased expression of integrins and genes regulating implantation.[19,20]

In later stage disease, in addition to the above defects, pelvic adhesions and endometriomas may impair oocyte release, block sperm entry into the peritoneal cavity or impair tubal transport. Women with later stage disease have reduced fecundity and poorer outcomes with artificial reproductive technology compared with earlier stage disease or women with unexplained or tubal factor infertility.[21,22]

In an effort to provide guidance to clinicians working with infertile couples, this document, produced by the Australasian CREI (Certificate of Reproductive Endocrinology and Infertility) Consensus Expert Panel on Trial evidence (ACCEPT) group, provides an Australasian consensus statement on the current management of endometriosis in infertile women. These recommendations may change as new evidence becomes available and will be updated as necessary.

Methods

MEDLINE, EMBASE, PubMed, the Cochrane Database of Systematic Reviews were searched using the terms 'endometriosis' 'endometrio$', AND 'infertility', 'subfertilty', 'IVF', '*in vitro* fertilisation', 'surg$' 'IUI', 'ART', 'down-regulation' and limited to humans and English language. The date of the last search was April 2012.

This document uses the NHMRC Evidence Hierarchy as outlined in Table 1

The ACCEPT Group have introduced the following nomenclature to define levels of agreement regarding individual statements within this and future documents.[23]

Consensus:

Unanimous	α
Unanimous with caveat	β
Majority	γ
No consensus	δ

Table 1 NHMRC levels of evidence

Level of evidence	Intervention
Level I	Systematic review of level II studies
Level II	Randomised controlled trial
Level III-1	Pseudorandomised controlled trial
Level III-2	A comparative study with concurrent controls
Level III-3	A comparative study without concurrent controls
Level IV	Case series with either post-test or pretest/post-test outcomes

All consensus statements derived by the authors from the search outlined earlier were modified as required and voted on by the CREI expert group in Sydney on 5 May 2011 and 4 April 2012. Those clinicians in attendance are listed below in Acknowledgements. All contributing ACCEPT Group clinicians were again invited to have input into the final statement before it was finalised by the authors.

Results

Medical treatment

Hormonal treatment

Spontaneous conception. A large meta-analysis of randomised trials evaluating the effect of ovarian suppression as compared to placebo or no treatment found no difference in spontaneous pregnancy or live-birth.[24]

Ovarian suppression with the oral contraceptive pill, GnRH agonists, medroxyprogesterone acetate or danazol is not recommended for patients wishing to conceive.

Assisted reproduction. Refer below to Assisted Reproduction Medical pretreatment.

Nonhormonal treatment – no inhibition of ovulation

1 Lipiodol – A randomised controlled trial (RCT) of uterine bathing and tubal flushing with lipiodol by hysterosalpingography versus no intervention, in 62 women with endometriosis and normal tubes and ovaries, showed improved clinical pregnancy rates with lipiodol (48% vs 10.8%; RR 4.44; 95% CI: 1.30, 10.5) and live birth rates (40% vs 10.8%; RR 3.7; 95% CI: 1.30, 10.50) at 6 months but no difference at 2 years.[6,25]

2 Pentoxifylline – This is an immune modulator and is postulated to have anti-inflammatory effects, a reduction in cytokines and improve blood flow and oxygen delivery. A Cochrane review of three RCTs comparing pentoxifyline to placebo showed no improvement in pregnancy rates (OR 1.54; 95% CI: 0.89, 2.66)[26] (Table 2).

Table 2 Summary of medical treatment alone of women with endometriosis desiring future fertility

	Grade of recommendation
Hormonal suppression of endometriosis does not improve spontaneous pregnancy rates	Level I evidence Consensus grade ∝
Hysterosalpingography with lipiodol improves short-term pregnancy rates (6 months) for women with a history of endometriosis	Level II evidence Consensus grade ∝
Pentoxyfilline (an immune modulator) does not improve spontaneous pregnancy rates	Level I evidence Consensus grade ∝

Surgical treatment

Surgical treatment of endometriosis aims to remove macroscopic endometriosis and restore normal pelvic anatomy. However, surgery may not be able to completely reverse the chronic inflammatory state or repair severe anatomical distortion. When measuring the effect of surgery is important to weigh up the benefits versus the harm.

The laparoscopic approach is favoured over laparotomy because of the advantages of minimal tissue damage, magnification, faster recovery and shorter hospital stay.[27]

Stage I–II

Spontaneous conception. There are two large RCTs comparing laparoscopic surgery for early stage endometriosis to diagnostic laparoscopy that show conflicting results. The Marcoux study in 1997 reported a large positive effect of surgery (OR pregnancy 2.06; 95% CI: 1.28, 3.33) and the Gruppo Italiano study reported no difference.[28,29] Meta-analysis of these two trials demonstrated an advantage of laparoscopic surgery compared with diagnostic laparoscopy in regards to live birth and ongoing pregnancy at 20 weeks (OR 1.64; 95% CI: 1.05, 2.57)[30] and the number needed to treat for one additional ongoing pregnancy is between 3 and 100. Similar outcomes are found with primarily ablative techniques or by excision.[31]

Assisted reproduction. There are no randomised trials comparing laparoscopic surgery to IVF for minimal endometriosis and infertility. There are no prospective RCTs comparing excision of stage 1–2 disease prior to IVF. A retrospective study of 661 women showed an improved IVF pregnancy rate in those who had diathermy of stage 1–11 endometriosis prior to ART versus those who had a diagnostic laparoscopy alone (40.1% vs 29.4% $P = 0.004$).[32] Unfortunately owing to its nature, this study has many areas of bias, and further prospective studies are needed.

Surgical technique. Although the recent RCT examining primary pain outcomes for laparoscopic excision versus ablation of endometriosis did not find any significant difference in pain outcomes,[33] there are no trials comparing excision of peritoneal endometriosis with ablation with the primary endpoint of pregnancy or fecundability. However, a number of trials have assessed the clinical outcomes in this situation. The aim of all excisional surgery should be to optimally resect all macroscopic disease within the safety constraints of each individual surgical setting. There are some authorities who contend that excision of endometriotic lesions is a superior technique to ablation based on:

1 Histological diagnosis
2 Complete resection of disease
3 Reduction in residual nonviable tissue and hence potential reduction in adhesion formation
4 The possibility of lower recurrence rates

Stage III–IV

There is no RCT or meta-analysis to assess the effect of surgery versus expectant management for moderate-severe endometriosis on pregnancy rates. There are many uncontrolled studies, confounded by bias, with differing results varying from a postoperative pregnancy rate of 30[34]–67%.[35]

Ovarian disease

Spontaneous conception. One small prospective study of seventy women with unilateral endometrioma demonstrated reduced ovulation from the affected ovary as compared with the unaffected ovary (31% vs 69%; 95% CI: 22%, 43% P value 0.002).[36] Further studies are needed to assess the impact of endometrioma on spontaneous conception.

Assisted reproduction. In the following paragraphs, surgery for endometriomas prior to IVF is discussed,

Surgical technique: Surgical options for the management of endometrioma include drainage, fenestration with ablation and excision of the endometrioma (cystectomy). A Cochrane review comparing excision to drainage and electrocoagulation of the cyst wall showed an increase in spontaneous pregnancy rates in women with subfertility with excision of the cyst with an odds ratio of 5.21; 95% CI: 2.04, 13.29.[37] In addition, there was a decreased rate of recurrence and no difference in response to gonadotrophin stimulation.

Pouch of Douglas and recto-vaginal lesions

Spontaneous conception. There is limited data assessing the effect of surgery on fertility. To our knowledge, there is only one controlled study by Vercellini *et al.*;[38] a nonrandomised study of 105 women comparing surgery with expectant management. This study found no difference in 12-month probability of conception (20.5% in surgical group and 34.7% in expectant $P = 0.12$).[38]

A large prospective cohort study of 500 women treated with laparoscopic rectal shaving of endometriotic lesions found that 57% of women wishing to conceive had

conceived naturally in a mean follow-up of 3.1 years.[39] The reported complication rates in this study included a 1.4% rectal perforation rate sutured laparoscopically and 0.8% ureteral injury rate (four patients, one requiring vesico-ureteral reimplantation).

A nonrandomised study by Stepinewska *et al.*[40] looked at the effect of removing bowel endometriosis and found that women who had a colorectal segmental resection for bowel endometriosis had a higher monthly fecundity rate (MFR) than women who had all disease excised except for bowel disease (MFR 2.3% resection of bowel disease vs 0.84% bowel disease left $P = 0.03$). However, the complication rate in the group having a bowel resection was significant: 3.2% anastomotic fistula, 1.6% ureteral lesion, 12.8% severe blood loss requiring transfusion and 25% of women had urinary retention requiring catheterisation for 1 month.

Assisted reproduction. A nonrandomised prospective cohort study by Bianchi *et al.* of 179 infertile women with deep infiltrating endometriosis and infertility examined the impact of surgery prior to IVF versus IVF alone. The pregnancy rate in the surgery group following IVF was 41%, and the no surgery group was 24% $P = 0.004$ suggesting a benefit to removing deep disease prior to IVF.[41] There were no reported major complications in the surgery group but one patient had a pudendal nerve injury requiring 6 months of physiotherapy.

Surgical technique. Excision of recto-vaginal or colorectal disease is major surgery with inherent morbidity and must only be undertaken after extensive counselling and by experienced surgeons. This surgery can reduce pain symptoms but may have a limited impact on fertility. The decision to perform surgery or to do IVF must be made on an individual basis primarily taking into account pain symptoms.

Anti-adhesion treatment

Although there is evidence that solid adhesion barriers such as Interceed (oxidised regenerated cellulose) and Gore-tex (polytetrafluoroethylene) reduce adhesion formation, there is insufficient evidence that this improves pregnancy or fertility rates.[42]

There is insufficient evidence that anti-adhesion fluid instillates reduce adhesion formation or improve fertility and pregnancy rates.[43]

Postoperative hormonal treatment

Surgery may not remove microscopic disease and for this reason hormonal treatments have been used in an attempt to suppress disease and prevent recurrence. There is conflicting data regarding the effect of postoperative ovarian suppression on future fertility. A meta-analysis of eight studies comparing surgery plus hormonal treatment versus surgery plus placebo or no treatment showed no difference in pregnancy rates (RR 0.84; 95% CI: 0.59, 1.18).[44] The hormonal treatments included GnRH agonists, danazol and medroxyprogesterone acetate.

However, an RCT of surgery plus 6 months of GnRH-analogue (GnRH-a) prior to three cycles of ART($n = 55$) versus surgery alone and three cycles of ART($n = 55$) demonstrated a significant improvement in pregnancy rate with IUI and a trend to an improved rate with IVF in the group treated with the GnRH-a (IUI cumulative PR 89% in GnRH-a group vs 61% in surgery alone $P < 0.05$, IVF/ICSI 75% in GnRH-a group vs 47% $P > 0.05$ in surgery alone group).[45] Further trials are required.

Second-line (reoperative) surgery

A systematic review in 2009 found three studies comparing pregnancy rates after second-line surgery. It demonstrated a halving of pregnancy rates after second-line surgery compared with first line surgery (22% for repetitive surgery, 40% after primary surgery OR 0.44; 95% CI: 0.28, 0.68).[46] The studies included were all comparative retrospective studies with a total of 124 women having second-line surgery. Possible reasons for poorer pregnancy rates after repeat surgery include the selection bias inherent to self selection of a subgroup of patients, the aggressive nature of disease that recurs, surgically induced de-novo adhesions or further damage to ovarian reserve.

There are two small retrospective studies comparing reoperation to IVF with inconsistent outcomes.[63,64] Pagidas *et al.*[47] reported a 9-month cumulative pregnancy rate of 24.4% in 18 women undergoing second-line surgery for stage III-IV disease and a crude pregnancy rate of 33.3 and 69.6% in 23 women undergoing one or two IVF cycles. Cheewadhanaraks[48] found a 12-month cumulative pregnancy rate of 20.5% in 32 women undergoing repeat laparotomy versus a clinical pregnancy rate of 12.5% in 24 women having a single cycle of IVF. The decision for repeat surgery or IVF must be made based on symptoms, the presence of complex cysts requiring histological diagnosis, age, ovarian reserve, the presence of male factor infertility, availability of skilled surgeons, cost and time-to-conception (Table 3).

Assisted reproduction

Intrauterine insemination

There are two RCTs which support the view that controlled ovarian hyperstimulation (COH)-intra-uterine insemination (IUI) is better than no treatment for endometriosis. Fedele *et al.* randomised 49 women to three cycles of COH-IUI or 6 months of timed intercourse (Fedele, 1992 #78). They found that the cycle fecundity rates were significantly higher in the COH-IUI group (0.15% vs 0.045%; $P < 0.05$), but not the cumulative pregnancy rates (37.4% vs. 24.0%). A much larger study by Tummon *et al.*[49] randomised 103 patients (311 cycles) and found that the cumulative live birth rate was 5-fold higher following COH-IUI (OR 5.6; 95% CI: 1.8, 17.4).

Nevertheless, there is strong evidence from a large number of observational studies that the outcomes

Table 3 Summary of recommendations for surgery in women with endometriosis desiring future fertility

	Grade of recommendation
Laparoscopic removal of minimal stage endometriosis may improve spontaneous pregnancy rates	Level I evidence Consensus grade ∝
Laparoscopic excision of endometriomata is superior to ablation with regards to spontaneous pregnancy rate	Level I evidence Consensus grade ∝
There is conflicting evidence to determine whether removal of recto-vaginal lesions improves spontaneous pregnancy rates	Level III evidence Consensus grade ∝
There is insufficient evidence to recommend the use of anti-adhesives to improve future fertility	Level I evidence Consensus grade ∝
There is insufficient evidence as to whether postoperative hormonal suppression improves natural conception on completion of therapy	Level I evidence Consensus grade ∝
Repeat surgery suggests less benefit with regards to pregnancy rates as compared to first line surgery	Level III evidence Consensus grade ∝

following COH-IUI in women with endometriosis are more unfavourable compared with women with other aetiologies.[50–56] The largest of these studies[55] analysed 14 968 cycles in 3371 couples and found that women with endometriosis had a 30% lower chance of achieving a pregnancy than women without endometriosis (adjusted OR 0.71; 95% CI: 0.54, 0.92).

It is less clear, however, whether surgery for minimal–mild endometriosis prior to COH-IUI improves the success rates. In a nonrandomised study by Singh *et al.*,[52] the monthly fecundity rate (MFR) for women with surgically treated endometriosis (average age 37.2 years) was 6.8% (live birth rate 6%) which was significantly lower ($P = 0.002$) than those in the idiopathic infertility group (average age 37.7 years) (MFR = 13.5%, LBR = 12.1%). In the study by Werbrouck *et al.*[57] on the other hand, the clinical pregnancy rate per cycle was comparable in women with previously treated minimal or mild endometriosis (21 or 18.9%, respectively) and in women with unexplained infertility (20.5%). It should be noted that the average age of the women in this study was lower (endometriosis: 30.8 years; idiopathic: 32.6 years).

In vitro fertilisation

Barnhart *et al.*[22] performed a meta-analysis of 22 observational studies. His systematic review concluded that women with endometriosis have poorer IVF outcomes than women with tubal infertility (OR, 0.56; 95% CI: 0.44, 0.70).

In addition, women with more severe disease had worse outcomes than women with minimal/mild disease (OR, 0.60; 95% CI: 0.42, 0.87). The authors concluded that the effect was not solely explained by changes in the endometrium, because the number of oocytes collected and the number of fertilised oocytes were lower in the endometriosis group.[22]

Medical pretreatment

With GnRH-analogue. To date, three RCTs[45,58,59] have been published looking at the effect of medical pretreatment with GnRH analogues prior to IVF. The underlying rationale being that the hypo-oestrogenic environment thus created, may reduce the inflammatory effects of the endometriosis on the reproductive system.

A systematic review[60] summarised the findings of these three RCTs, which collectively comprised 165 women with infertility and severe endometriosis. The pretreatment with GnRH-a significantly increased the live birth rate compared with no pretreatment (OR 9.19; 95% CI: 1.08, 78.22).

There was obvious heterogeneity in the length of the GnRH-a pretreatment (3–6 months), each of the studies was relatively small and there a number of other methodological concerns[61] that cast some doubt on the strength of the conclusions, also reflected in the very wide confidence interval (95% CI: 1.08, 78.22) around the point estimate.

With the oral contraceptive pill (OCP). There are no RCTs available that address the question of the effectiveness of OCP pretreatment prior to IVF. There is one observational study by De Ziegler *et al.*[62] They hypothesised that the purported beneficial effects of GnRH-a pretreatment were more linked to ovarian suppression, than with a low-oestrogen environment *per se*. Given the lower side effect profile, they investigated whether pretreatment with the OCP is a useful alternative. A total of 286 women with endometriosis and 509 women without clinical evidence of endometriosis were allocated in a nonrandomised way to either no pretreatment or 6–8 weeks of OCP pretreatment. Their findings suggest that ART outcomes following OCP pretreatment in women with endometriosis are comparable with the outcomes of age-matched controls without endometriosis.

Surgery for endometriomas prior to IVF

The benefit of surgical treatment of endometriomas prior to IVF is still hotly debated. A number of concerns have been raised as arguments for the removal of endometriomas prior to IVF. However, the available evidence appears to alleviate these concerns.

1 Reduced ovarian responsiveness with COH

One of the better prospective controlled studies by Almog *et al.*[63] compared 81 women with a unilateral

endometrioma and 162 age-matched women with no endometriosis. All women were followed during their first IVF cycle. There were three main conclusions: (i) there is no correlation between the size of the endometrioma and the number of oocytes collected, (ii) the same number of oocytes were retrieved from the affected ovary (7.7 ± 1.0) and the opposite ovary (8.5 ± 0.9) and (iii) the total number of retrieved oocytes was the same in women with (11.9 ± 0.8) and without endometriosis (11.4 ± 0.5).

2 Risk of growth/rupture with COH
Benaglia *et al.*[64] followed 48 women with an endometrioma who had failed to become pregnant following IVF. They were rescanned again 3–6 months later to evaluate the growth of the endometrioma. The median (interquartile range) volume of the cysts before (3.9 mL; 2.9–7.9) and after the follow-up (4.9 mL; 2.4–9.9) was not significantly different. These volumes correspond with mean diameters of 9.8 and 10.5 mm, respectively.

3 Risk of abscess formation
Although there are several case reports, which describe abscess formation following egg collection in women with an endometrioma, it is unclear what the true incidence is. The only prospective study to date[65] to give us guidance did not observe the complication in a series of 214 IVF cycles in women with endometriomas.

4 Risk of malignancy
The potential for malignant transformation is always a serious concern. However, the question is whether this is a justification for the excision of every endometrioma. It can be calculated that one extra ovarian cancer will occur for every 10 000 women with endometriosis.[66] Put differently the lifetime probability of developing ovarian cancer increases from 1/100 to 2/100 or, in other words again, a woman with untreated endometriosis has a 98%, instead of a 99% probability, of never developing an ovarian malignancy.[67] It is doubtful that the risks of exposing every women with an endometrioma to an operative laparoscopy can be offset by the early detection of the very rare endometrioma-related malignancy.

The debate seems to be turning and concerns are now raised about the blanket excision of endometriomas in infertile women.

Firstly, there is evidence that ovarian surgery reduces the number of oocytes retrieved, reduces peak oestradiol levels, and increases total FSH requirement.[68,69] Ovarian surgery has also been reported in a prospective study to lead to complete ovarian failure in the operated ovary in 13% of the cases.[70]

Secondly, and more importantly, there appears to be no discernable effect on pregnancy rates. A recent systematic review[71] found that surgery (aspiration or cystectomy) versus expectant management showed no evidence of a benefit for clinical pregnancy with either technique. Aspiration was associated with a greater number of oocytes retrieved (MD 0.50; 95% CI: 0.02, 0.98) compared with expectant management, whereas cystectomy was not different in this respect. It should be noted that this systematic review overlooked the fact that the RCT by Demirol *et al.*[69] compares surgical excision against aspiration of the endometrioma during the oocyte collection procedure. It can thus not be regarded as a trial comparing excision versus expectant management, given that an effect of cyst aspiration on subsequent embryo implantation cannot be excluded.

Another meta-analysis of five nonrandomised trials found that excision of an endometrioma may be no better than no treatment prior to IVF.[72]

Other treatment options were also summarised in the systematic review by Benschop *et al.*[71] GnRH agonist and GnRH antagonist treatment in women with endometriomas resulted in similar clinical pregnancy rates. As previously also reported in patients without endometriosis, the number of mature oocytes retrieved was greater with GnRH agonists (MD −1.60; 95% CI: −2.44, −0.76).

Obviously, there are situations when removal of an endometrioma is warranted on clinical grounds such as for management of pelvic pain or spontaneous rupture, but for infertility alone, there is no clear cut answer. The hypothetical and evidence-based risks and benefits of the management of endometriomas prior to ART are summarised below in Table 4.

Does ART increase the recurrence rate of endometriosis?

Two observational studies have been published that have attempted to answer this question.

The first one is a relatively small retrospective cohort study by D'Hooghe *et al.*[73] This study followed up 67 patients with stage III or IV endometriosis who underwent pelvic reconstructive surgery and subsequently started fertility treatment with either IVF only (n = 39), both IVF

Table 4 Risks and benefits of observational and surgical management of endometriomas

Observational	Surgery
Benefits	
Avoid surgery	Exclude malignancy
Lower FSH doses	Relieve symptoms
Increased E2	Reduce the risk of cyst complications
Increased follicles	Facilitate transvaginal access to ovarian follicles
Risks	
Pain	Ovarian failure because of destruction of normal ovarian tissue
No histological diagnosis	Reduced number of eggs collected
Pelvic infection following egg collection	Risks of surgery

Table 5 Summary of recommendations for assisted reproductive technology (ART) in women with endometriosis desiring future fertility

ART in women with endometriosis desiring future fertility	Grade of recommendation
COH-IUI is associated with higher pregnancy rates than no intervention	Level I evidence Consensus grade β Caveat: There is an increase in multiple birth with this treatment
Women with endometriosis have lower clinical pregnancy rates following COH-IUI compared to women with other aetiologies where COH-IUI is indicated	Level II evidence Consensus grade ∝
Women with endometriosis have lower clinical pregnancy rates following *in vitro* fertilisation compared to women with other aetiologies and the effect is greater with increasing severity of disease	Level I evidence Consensus grade ∝
Pre-treatment with GnRH analogues for at least 3 months improves subsequent *in vitro* fertilisation outcomes	Level I evidence Consensus grade β Caveat: Poor quality study with a wide confidence interval
There is insufficient evidence that pre-treatment with the OCP prior to *in vitro* fertilisation improves pregnancy rates	Level III-2 evidence Consensus grade ∝
There is insufficient evidence to recommend the surgical treatment of endometriomas prior to *in vitro* fertilisation to improve pregnancy rates (refer to text for pros and cons)	Level II evidence Consensus grade α
In vitro fertilisation treatment does not increase the recurrence rate of endometriosis symptoms	Level III-3 evidence Consensus grade γ

and IUI in different cycles (n = 11), or IUI only (n = 17). The recurrence rates after 21 months was highest in the IUI only group (70%) and significantly different from the two other groups: women treated with both IVF and IUI in different cycles (43%) and those treated with IVF only (7%). The authors attempt to explain this result by suggesting that (i) more women in the IVF group may have had blocked tubes (although this does not explain the lower recurrence risk in the IUI and IVF group) and (ii) the GnRH agonist down-regulation may have had a suppressive effect.

The second study by Benaglia *et al.*[74] followed 189 endometriosis patients for a median duration of 34 months (interquartile range: 21–52) since their first IVF cycle. Of these, 41 women (22%) experienced a recurrence as defined by the authors: the need to undergo surgery or hormonal treatment despite an ongoing desire to achieve a pregnancy. Rather than using a control group, the authors hypothesised that the impact of IVF could be measured in the number of cycles these women had undertaken and/or in the degree of ovarian response during ovarian stimulation. This retrospective study did not identify any association between the number of cycles and disease relapse. The adjusted OR for recurrences according to the number of started cycles was 0.92 (95% Cl: 0.77, 1.10) per cycle. In addition, the risk of recurrences was not lower in women with a compromised ovarian reserve, again arguing against an adverse influence of the hormonal environment during ovarian hyperstimulation on endometriosis growth (Table 5).

Conclusions

Endometriosis is common in women with subfertility and can affect fertility on many different levels from inducing a local inflammatory state and decreasing endometrial receptivity, to causing mechanical obstruction and altering sexual function. Medical treatment of endometriosis does not improve spontaneous pregnancy rates, whereas there is some evidence that surgery for mild endometriosis does. There is conflicting evidence regarding removal of endometriomas owing to the potential impact on ovarian reserve, but there are also significant benefits to this surgery, including a possible reduction in pain. Continued research is required to assess the value of resection of recto-vaginal disease and repeat surgery. Assisted reproduction improves pregnancy rates as compared to no treatment, but the pregnancy rates are lower than for women without endometriosis. Medical, surgical and assisted reproductive treatments do not need to occur in isolation, and many women may benefit from a combination of approaches.

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