Endometrioma, fertility, and assisted reproductive treatments: connecting the dots

Gustavo N. Cecchino[a,b,c] *and Juan A. García-Velasco*[b,c]

Purpose of review
Surgery has traditionally been the primary treatment option for endometriosis-related infertility of any phenotype. However, advances and refinements of assisted reproductive technologies (ART) permit a more conservative approach in many scenarios. This review summarizes the latest findings in the field of reproductive medicine, which have supported a paradigm shift towards more conservative management of ovarian endometrioma.

Recent findings
The presence of ovarian endometrioma *per se* is likely to impair ovarian reserve and alter ovarian functional anatomy. Conventional laparoscopic surgery is associated with significant risk of additional damage, and less invasive treatment approaches require further evaluation. With regard to infertile women with ovarian endometrioma who are scheduled for ART treatment, current data indicate that prior surgical intervention does not improve ART outcomes, and that controlled ovarian hyperstimulation (COH) does not affect quality of life or pain symptoms.

Summary
Reproductive medicine physicians frequently encounter patients with ovarian endometrioma. The current evidence does not support the postponement of infertility treatment in favour of surgery, except in cases with severe symptoms or to improve follicle accessibility. Although these patients may exhibit diminished ovarian response to COH, their endometrial receptivity, aneuploidy rates, and fertility outcomes are similar to healthy controls. Surgery for ovarian endometrioma provides no benefits in ART treatments.

Keywords
assisted reproductive techniques, endometriomas, endometriosis, infertility, IVF

INTRODUCTION

Nearly 10% of women develop endometriosis during their reproductive years [1]. Although it is a benign disease, endometriosis can negatively impact a woman's health and quality of life. Cross-sectional studies suggest a causal relationship between endometriosis and infertility, although the reported risk estimates widely vary [2]. A recent analysis of a large ongoing prospective cohort of 58 427 women detected a two-fold increased risk of infertility among lean women of less than 35 years of age with laparoscopically confirmed endometriosis. However, subgroup analyses of women over 35 years old or with a BMI of at least 25 kg/m^2 did not permit an unequivocal conclusion due to confounding factors [3▪].

Patients struggling with endometriosis often pursue assisted reproductive technologies (ART) due to fertility issues. Ovarian endometrioma is the most prevalent phenotype, affecting about 20–40% of women with endometriosis [4,5]. Ovarian endometrioma management is challenging and controversial, especially in the context of ART. For a long time, surgery has been considered the primary treatment to overcome infertility in cases of ovarian endometrioma. However, advances in basic science and clinical evidence have supported a paradigm shift, such that more conservative management is now recommended.

In the present review, we aim to assess the latest findings concerning fertility issues, endometrioma, and assisted reproduction.

[a]Department of Gynecology, Federal University of São Paulo, São Paulo, São Paulo, Brazil, [b]Department of Gynecology and Obstetrics, Rey Juan Carlos University and [c]IVIRMA Madrid, Madrid, Spain

Correspondence to Gustavo N. Cecchino, IVI-Madrid, Rey Juan Carlos University, Madrid, Spain. Tel: +34 911 802 900; e-mail: gusta.nardini@gmail.com

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KEY POINTS

- Endometriomas induce chronic molecular changes that negatively impact ovarian reserve and function.
- Surgical excision of ovarian endometrioma by any technique clearly affects ovarian reserve, especially in cases of bilateral and recurrent endometriomas.
- Surgery performed prior to ART treatment does not improve reproductive outcomes, but rather increases the time to pregnancy and the risks and costs.
- COH does not affect quality of life or endometriosis-related pain symptoms.
- Less invasive approaches to ovarian endometrioma treatment must be further evaluated in randomized clinical trials.

IMPACT OF ENDOMETRIOMAS ON OVARIAN FUNCTION AND RESERVE

Few studies have been focused on determining the exact mechanisms through which endometriomas presumably impair normal ovarian physiology. Early investigations suggested that ovarian endometrioma was associated with reduced spontaneous ovulation rates [6,7], with the ovulation rate inversely proportional to the number of endometriotic ovarian cysts [7]. Importantly, these studies had a small sample size and involved patient monitoring for only a few ovulatory cycles. Leone Roberti Maggiore *et al.* [8] recently investigated a large prospective cohort, analysing over 1000 menstrual cycles. They reported similar ovulatory rates among affected ovaries regardless of the number and size of endometriomas. They also observed a high spontaneous pregnancy rate during the follow-up period [8]. Thus, it is reasonable to assume that ovulatory function is preserved in cases of ovarian endometrioma.

Accumulating evidence suggests that ovarian endometrioma alone may directly undermine ovarian reserve. Prior to surgery, women with ovarian endometrioma show diminished serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) compared with healthy counterparts, patients with tubal factor infertility, or patients with other benign ovarian cysts [9,10]. Similarly, reduced AFC has been reported in endometrioma-containing ovaries compared with the contralateral unaffected ovaries [11]. Conversely, Nieweglowska *et al.* [12] reported that AMH levels were significantly lower than normal only in cases of bilateral ovarian endometrioma, although a moderate effect was observed in unilateral ovarian endometriosis.

Some studies have included histopathological analysis of surrounding cortical specimens obtained during surgical ovarian endometrioma removal, which has revealed decreased follicular density and vascular abnormalities [13,14]. Indeed, up to 16% of such ovarian cortex specimens have exhibited a complete absence of follicles [13]. From a molecular perspective, the distinct detrimental events correlated with ovarian endometrioma could independently contribute to cytotoxicity-induced ovarian damage. Unsurprisingly, augmented oxidative stress appears to play a key role [15]. Convincing evidence suggests that endometrioma is likely induces a chronic decrease of ovarian reserve.

CONCERNS ABOUT SURGICAL EXCISION OF ENDOMETRIOMAS

Laparoscopic treatment of ovarian endometrioma was first described in 1986 [16]. Since then, laparoscopic cystectomy has become the gold standard treatment for ovarian endometrioma with surgical indication [17,18]. Nevertheless, several aspects relating to surgical management of endometriomas remain controversial, and the consequences to future fertility are not fully understood.

During the laparoscopic extirpation of endometriotic ovarian cysts via the stripping technique, over 50% of cases result in unintentional removal of healthy ovarian parenchyma [19]. The amount of ovarian tissue removed is directly proportional to the endometrioma size [20]. This frequently leads to follicle pool loss, mostly during hilar dissection, in which primary and secondary follicles have been observed in 85% of the specimens [21,22]. It remains unclear whether these follicles are fully functional, and if their capacity to grow is preserved in such a fibrotic area.

Investigations have shown no benefit of preoperative medical treatment compared with surgery alone [23]. Moreover, presurgical medical therapy carries an independent risk of removing normal ovarian tissue [24]. This risk is related to the surgeon's experience; however, even experienced specialists cannot guarantee that ovarian reserve will not be harmed [25,26].

Regarding surgical technique, excisional therapy is preferred over drainage and ablation. Excisional therapy is superior in terms of lower rates of recurrence of both endometrioma and pain symptoms, as well as increased subsequent spontaneous pregnancy rate [18]. At this time, we believe that conservative laparoscopic excision is the best option for patients having a precise indication for surgery. Notably, a systematic review and meta-analysis by Deckers *et al.* [27▪] suggested that nonthermal haemostasis may

minimize ovarian reserve damage, which is especially relevant for couples with reproductive goals. Further studies are needed to evaluate alternative haemostatic methods.

In 2010, Donnez *et al.* [28] and Muzii and Panici [29] proposed a modified procedure that theoretically combines the advantages of excisional therapy and drainage and ablation. In their method, the endometrioma is almost completely approached by excisional cystectomy, except for the area close to the hilus. This region is approached by ablation using either bipolar coagulation or CO_2 laser, thus ensuring maintenance of functional ovarian stroma [28,29]. Five years after its first description, this combined technique was compared with laparoscopic cystectomy in a multicentre randomized controlled trial (RCT) [30]. Women with bilateral endometriomas underwent conventional cystectomy in one ovary and combined surgery in the contralateral gonad, with random assignment. The two techniques were associated with similar endometrioma recurrence rates and ovarian reserves after 6 months of follow-up [30]. This RCT had several critical limitations, including the small sample size, limited follow-up period, and the facts that ovarian reserve was not the primary outcome and was only assessed by AFC. It would be valuable to analyse the preoperative and postoperative levels of both AMH and AFC.

Multiple studies demonstrate that surgical treatment of ovarian endometrioma diminishes serum AMH concentrations [26,31–34]. A systematic review and meta-analysis that included only prospective cohorts and RCTs concluded that surgical treatment is typically followed by a significant fall in AMH levels, which is sustained for at least 6–9 months and is apparently correlated with endometrioma size [35]. Curiously, AFC was unaffected by surgery in that analysis [35]. Likewise, the systematic review and meta-analysis by Muzii *et al.* [36] also found no postsurgical AFC declination, and in fact demonstrated lower AFC in patients with ovarian endometrioma before any surgical treatment [36]. AFC must be cautiously evaluated in women with endometrioma, as findings indicate that AFC might be underestimated in this population. Thoughtful comments regarding Muzii's meta-analysis have been published elsewhere [37–39].

All of the above-mentioned meta-analyses show remarkably high heterogeneity. Nonetheless, we think that data derived from the top-quality studies clearly suggest that ovarian reserve is significantly impaired following surgery for ovarian endometrioma. In addition, a systematic review by Somigliana *et al.* [40] identified several independent risk factors for postoperative AMH decline, including bilateral endometriomas, reduced preoperative AMH levels, and presence of normal ovarian tissue in surgical specimen. It can also be presumed that repeated surgeries for recurrent endometriomas will incur greater damage [41]. The results of the only study with a follow-up period beyond 1 year after surgery for ovarian endometrioma confirm the long-term declination in ovarian reserve [42]. Other potential issues related to surgery for ovarian endometrioma include reduced ovulation rates, modification of ovarian artery blood flow, and the inherent risks associated with any surgery [6,43].

WHEN IT COMES TO ASSISTED REPRODUCTIVE TECHNOLOGIES TREATMENTS...

When scheduling IVF for infertile patients presenting with ovarian endometrioma, clinicians must carefully consider whether to perform surgical treatment prior to IVF. Extensive evidence indicates that surgery can lead to quantitative and qualitative injuries. Moreover, numerous reports describe a poorer ovarian response to controlled ovarian hyperstimulation (COH) among women who have undergone surgery for ovarian endometrioma [44–47]. Tang *et al.* [48] found a statistically significant decrease in the number of oocytes retrieved after surgery for ovarian endometrioma, but only when the operated endometriotic cyst was larger than 4 cm. Following adjustment for potentially confounding variables, this difference remained significant and a receiver operating characteristic curve revealed an inverse relationship between endometrioma size and the recovery of more than four oocytes [48]. Other investigations show similar COH responses between women with previous surgery versus those with intact endometrioma, and between operated versus nonoperated gonads from the same patient [49–51]. However, a complete lack of COH response is reported in up to 13% of operated patients [52].

When taking into account only systematic reviews and meta-analysis that compare surgical treatment versus no surgery before IVF, the conclusions remain controversial. Regarding ovarian response to COH, one meta-analysis reported no between-group differences [53], another found that the operated group required higher gonadotropin doses and showed fewer oocytes collected [54▪], and a third meta-analysis only demonstrated the need for increased gonadotropin doses after surgery [55]. Only one RCT has investigated whether pre-IVF cystectomy improved reproductive outcomes, and it did not demonstrate any benefit of surgery, instead reporting that surgery was associated with

similar fertilization, implantation, and pregnancy rates along with a decreased ovarian response to COH [47]. In general, most studies have found comparable outcomes with regard to these parameters as well as the number of embryos, live birth rates (LBR), and miscarriages rates [46–48,50,51, 53,54▪,55].

One interesting study evaluated reproductive outcomes after single embryo transfer in women who previously underwent unilateral ovarian endometrioma excision and found similar pregnancy potential between embryos derived from oocytes of the operated gonad versus those derived from the contralateral healthy ovary [56]. Another investigation revealed that women with diminished ovarian reserve (DOR) secondary to endometrioma cystectomy exhibited poorer reproductive outcomes than women with idiopathic DOR, and these results remained unchanged in a subgroup analysis of cases respecting the Bologna criteria [57]. This study had several important limitations, including its retrospective design and the definition of DOR based on pre-COH AMH levels of less than 2 ng/ml without knowing the presurgical AMH concentration. A recent retrospective analysis of a large prospectively managed database highlighted that surgery for ovarian endometrioma was independently associated with lower pregnancy rate [58].

These data, together with the results of studies examining reproductive outcomes after IVF in nonoperated patients with ovarian endometrioma, clearly suggest that surgical excision must be limited to selected patients. Although endometrioma *per se* could impact the responsiveness to COH [59–61], the presence of unilateral ovarian endometrioma is not necessarily associated with adverse outcomes. Importantly, unilateral ovarian endometrioma does not seem to affect oocyte competence, embryo quality, implantation rate, pregnancy rate, or LBR [59,62]. These findings have been reaffirmed in at least three meta-analysis by distinct authors [55,63,64].

Among women with ovarian endometrioma, up to 28% develop bilateral disease [65]. Limited data are available regarding the surgical consequences to reproductive health and IVF outcomes in this patient group. Unoperated bilateral endometriomas reportedly have minor effects during ART treatments [66,67]. Conversely, bilateral cystectomy is associated with a significant deterioration of ovarian response to COH and worse post-IVF outcomes [68]. In these cases, clinicians must consider the possibility of early-onset or late-onset ovarian insufficiency, as well as the increased risk of earlier menopause [69–71].

Less invasive approaches to ovarian endometrioma treatment have been explored as alternatives to conventional laparoscopic procedures; however, none have proved to be superior. Endometrioma aspiration before ART treatment did not enhance the ovarian response to COH or improve reproductive outcomes [72]. Cohen *et al.* [73▪] recently performed a systematic review with meta-analysis of the use of sclerotherapy for ovarian endometrioma, and reported that this simple and safe strategy is not inferior to laparoscopic cystectomy in terms of endometrioma recurrence, pain relief, and reproductive outcome after IVF. However, no benefit was detected in women who underwent sclerotherapy before IVF compared with women with intact endometrioma [73▪]. Although the findings are promising, further well designed studies are needed to draw definitive conclusions.

Over the past few years, several studies have focused on aspects somehow neglected by medical research so far. We comprehend that they are of great interest for patients suffering with endometriosis and scheduled for ART treatments. In 2016, an observational cohort study reported that COH does not aggravate the disease based on pain symptoms and quality-of-life scores [74]. Seyhan *et al.* [75] used three-dimensional ultrasound examination to accurately assess endometrioma size during COH, and verified slight but significant endometrioma growth that had no negative clinical impact [75]. In a pilot study, Garcia-Velasco *et al.* [76] investigated transcriptomic gene signatures during the implantation window in the endometrium of women with endometriosis. Using the endometrial receptivity array test, they demonstrated that endometrial gene signatures in these patients do not differ from healthy controls [76]. Similarly, a large retrospective cohort compared the aneuploidy rates of over 1800 blastocysts from patients with endometriosis versus over 23 000 blastocysts from age-matched patients without endometriosis and determined that aneuploidy rates did not differ between these groups [77▪]. This evidence can help alleviate common patient concerns.

CONCLUSION

The currently available evidence indicates that ovarian reserve and response to COH may be impaired by ovarian endometrioma, but that surgery does not lead to improved fertility outcomes. Thus, we comply with the current American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology guidelines regarding endometriosis management. Patients scheduled to undergo ART treatments should only undergo prior surgical treatment in cases of severe pelvic pain or reduced accessibility of follicles [78,79]. This practice reduces the time to pregnancy, as well as

minimizes the risks and costs. Importantly, whenever there is any suspicious of malignancy, ovarian endometrioma must be removed and submitted for proper anatomopathological analysis. In cases of young women suffering from bilateral disease with a clear surgical indication, it would not be inappropriate to offer fertility preservation before surgery.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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