Effect of endometrioma and its surgical excision on fertility (Review)

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Abstract. Endometrioma is the cystic lesion of ovaries originating from endometrial glands and stroma; it is identified in 17-44% of patients with endometriosis. Numerous existing studies have reported the association between endometrioma and infertility. However, an absolute cause-effect association requires further confirmation. Available evidence has suggested that ovarian reserve may be impaired by spatial occupation influences, local reaction or both, affecting the reproductive health of females. Given the increased focus on the pathophysiological mechanisms of endometrioma, surgical excision has commonly been considered to avoid further ovarian damage. However, the potential adverse effect of this surgery on the ovarian reserve has recently become a focal point. Whether or not surgical excision can facilitate subsequent conception in young females planning to be pregnant is controversial. As shown in the present review on the effects of endometrioma and its removal in females requiring assisted reproductive technology, prior surgery for endometrioma may not improve assisted fertility results and may further decrease the number of oocytes retrieved in the affected females. Subsequent studies are needed to ascertain the optimal management of infertility in the setting of endometriomas.

Contents

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1. Introduction

Ovarian endometrioma (OMA) is a clinical phenotype affecting 17-44% of females with endometriosis (1). Although the underlying pathogenesis of OMA remains to be elucidated, three major theories were developed to expound the origin of endometriomas. According to Hughesdon, endometriomas are pseudocysts that accumulate from menstrual debris by bleeding from active implants located at the site of inversion (2). Nisolle and Donnez proposed an additional theoretical point with endometriomas originating from the metaplasia of the invaginated ovarian coelomic epithelium (3). Jain and Dalton reported that endometriomas can originate from the ovarian follicle, but also confirmed that the fluid origin in the cysts remains unclear (4). Based on clinical appearances and histology-related testing, the clinic-related types of endometriomas include: i) Protopathic endometrioma-true endometrioma origin; and ii) secondary endometrioma-follicular or luteal ovarian cysts covered or invaded by cortical endometriotic implants or by major endometrioma (5). In this review, the term 'endometrioma' is specific to protopathic endometrioma (without lesions identified in other locations).

Based on the existing data, 30-50% of females with endometriosis experience fertility issues and typically present with endometriomas during infertility screening (6). The exact mechanism by which endometrioma causes infertility remains to be elucidated. Researchers suggested that there is a decline in the ovarian reserve in patients with OMA, which may result from the formation of endometrial cysts and associated structural variations. Since endometriomas often do not respond well to medical therapy, emphasis has been placed on surgical excision to improve fertility. Nevertheless, surgical removal of these cysts has been found to reduce ovarian reserve. Thus, the controversy surrounding the treatment of endometrioma and the uncertainty surrounding infertility, especially among females having received assisted reproductive technology (ART) are highlighted. Given the high degree of attention and dispute concerning this issue, little evidence exists to provide robust guidance to clinicians. As such, this area of management remains a clinical challenge for doctors until now. This article

will give an overview of the recent literature investigating the association between endometrioma and fertility. The aim of the present study was to find evidence supporting or rejecting the hypothesis that endometrioma may cause infertility, and to demonstrate whether surgical excision of endometriotic cyst can improve fertility outcomes of spontaneous and assisted conception.

2. Endometrioma and ovarian physiology: Pathogenic considerations

An increasing number of studies focused on assessing the potential harm of endometrioma to ovarian physiology. The harmful effects of endometrioma are supported by numerous morphological and functional characteristics that physiologically distinguish affected ovaries from healthy ovaries (7). This is based on evidence derived from a pathophysiological view, in part translating the deleterious influence exerted by endometrioma on close ovarian cortical tissue, without relying on mere mechanical stretching.

One important explanation supporting the impairment of ovarian physiology is based on the cyst contents, representing an underlying toxicity source to the surrounding healthy tissue (Fig. 1). The molecular environment inside the cyst is an abundant source of inflammatory molecules, iron, reactive oxygen species (ROS), transforming growth factor-β (TGF-β) and proteolytic enzymes in higher levels when compared with benign cysts (7). Firstly, the contents are considered to be able to induce a high frequency of somatic mutations in the cells that internally line the cyst, potentially inducing tumorigenesis (8,9). Secondly, the healthy ovarian cortex surrounding the endometrioma has higher levels of oxidative stress than other benign cysts (10). TGF-β acts in a synergistic manner with ROS to promote a fibrogenic response, and proteolytic substances may degrade the adjacent areas, followed by reduced cortex-specific stroma (11). The ovarian stroma supplies blood of the primordial follicles via its capillaries and works synergistically with other components to induce the transition from primordial to primary follicles (7). Thus, the loss of a cortex-specific matrix should be considered for its potentially harmful effects on follicular development, as it reduces the blood supply to the follicles and decreases the secretion of growth factors from stromal cells (12). Moreover, the high levels of ROS may inhibit ovarian angiogenesis and cause capillary loss, based on direct or indirect methods, which reflects a decrease in blood perfusion and impaired follicular maturation (13). Additionally, imbalanced oxidative stress has been confirmed to be an underlying reason for necrosis in early follicles (14). Due to the increasing focus on the physiological characteristics of affected ovaries, cyst formation and associated functional variations in the adjacent ovarian cortex may partially account for the reduced ovarian reserve.

Variations of ovarian follicle function and oocyte quality in affected females have garnered attention. Follicular fluid (FF) might reflect the microenvironment during follicle and oocyte growth. It is speculated that several biochemical features of the FF in the proximity of the oocyte may be vital in determining oocyte quality (15). Peritoneal endometriosis has been demonstrated to affect follicular growth by altering the components of the FF, whereas whether endometriomas also creates an unfavorable FF environment as observed with peritoneal endometriosis is a subject of debate (16). In a previous study, elevated iron levels were reported in follicles in proximity to an endometrioma compared with OMA-distal follicles and contralateral follicles, whereas this report did not assess the oxidative stress status and antioxidative potentials of FF (17). Moreover, Nakagawa *et al* (18) concluded that OMA only slightly affects the follicle growing environment as a similar oxidative stress status was identified in the FF in cases with unilateral endometrioma and those without the disease. To be specific, although iron is likely to diffuse from endometriomas into the surrounding ovarian tissue, iron-induced oxidative stress response is limited by the partitioning function of several feasible biology-related systems, such as ferritin storage (19). This appears to only slightly impact ovarian function and oocyte quality. According to Opøien *et al* (16), the levels of interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12 and tumor necrosis factor were comparable between follicles adjacent to endometriomas and those in control subjects, thereby excluding variations that support inflammation. Moreover, Liang *et al* (15) determined the influence of endometrioma cystectomy on cytokines in the follicular fluid and concluded that OMAs display no correlation with cytokine profiles in the FF of infertile females. Overall, the findings of this study (15) indicated that endometrioma is not likely to affect in women with infertility as a result of inflammation. However, evidence supporting or contradicting an effect of endometrioma on ovarian function from both a clinical and a biological perspective is limited, and subsequent research is required to elucidate this important issue (20).

3. Endometrioma and ovarian reserve

Ovarian reserve is defined as the number and quality of follicles in the ovary at any set time (21). The hypothesis that endometrioma can impact ovarian reserve was established when histology-related research hypothesized that growing cysts, stretching the cortical tissue, might cause structural variations and circulation impairment, possibly leading to a decrease in the primordial follicle cohort in affected ovaries (22). The effects of OMA (without previous surgery for OMA) on the ovarian reserve remain to be elucidated. The most reliable and extensively used ovarian reserve marker has been the level of anti-Mullerian hormone (AMH) due to its consistency throughout the menstrual cycle and following hormonal variations or treatments (23,24).

In a recent systematic review and meta-analysis, 17 papers recruiting 968 females with endometrioma and 1,874 controls were involved in the pooling process. The results revealed that AMH levels were noticeably lower in females with endometrioma in contrast to control groups (healthy ovaries and/or benign ovarian cysts) (25). As has been detailed in previous publications (26-28), the presence of OMA is correlated with a decrease in AMH levels and adversely affects the ovarian reserve. However, numerous researches call into question the adverse influence of endometrioma on the ovarian reserve. Streuli *et al* (29) reported that AMH levels were downregulated only in subjects having undergone surgery independently of the presence of current endometriomas. Nieweglowska *et al* (30) reported that significantly decreased AMH levels were

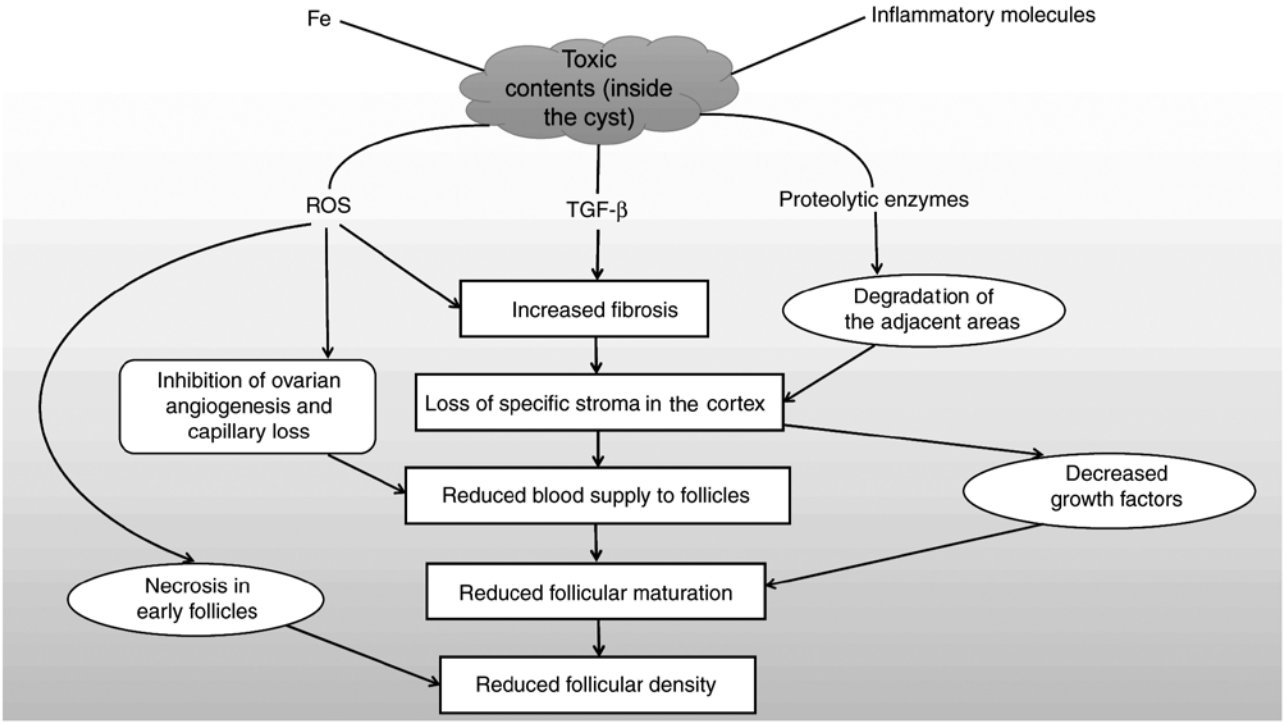

Figure 1. Overview of the underlying mechanism of OMA-related reduction in ovarian function. OMA, endometrioma; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; Fe, iron.

observed only in females with bilateral endometrioma, rather than in those with unilateral endometrioma. Similarly, Esinler *et al* (31) reported that endometriomas with ≤3 cm in diameter did not impact the ovarian reserve. Of note, data from females with unilateral endometrioma are poorly informative, since the contralateral intact ovary compensates for ovarian function and fertility potential (17). Since larger cysts may be associated with lower levels of AMH (32), a relatively small cyst may not cause AMH levels to be significantly altered. The aforementioned information may reveal that impairment may progress along with endometrioma development and growth, although its mechanism remains to be clarified.

4. Surgical excision of endometrioma and ovarian reserve

Clinical management of patients with endometrioma has been the subject of controversy, since the development and natural progression of endometriomas requires further clarification. A recent study suggested that females with endometrioma exhibited a progressive decline in serum AMH levels, faster than that in age-matched healthy females (33). Given the pathogenesis of endometrioma and its putative effects on the ovarian reserve, early diagnosis and subsequent early treatment are the options to avoid further ovarian injury and preserve ovarian reserve function (34,35), although the exact efficacy of this strategy has not been elucidated. Laparoscopic cystectomy of endometriotic ovarian cysts is currently considered the standard therapy for pain relief, and is performed to reduce the recurrence rate and increase the spontaneous conception rate among patients with endometrioma (36). At present, the role of surgical excision of endometriomas has been challenged by evidence indicating that the damage resulting from cystectomy may negatively affect the postoperative ovarian reserve.

The deleterious effect of cystectomy for OMA on ovarian reserve has been reflected by a further decline in AMH levels following operation (37-39). As shown in a meta-analysis regarding hemostatic approaches during surgery, the use of bipolar coagulation rather than suturing may partially decrease the ovarian reserve (40-42). Whether the inflicted damage is associated with the use of electrocautery or the procedure itself remains controversial. However, Shao *et al* (43) suggested that the ovarian reserve was significantly reduced when suturing technology was used as a method of hemostasis during endometrioma resection. A study conducted by Song *et al* (44) suggested that laparoscopic cystectomy for endometriomas can reduce the ovarian reserve, regardless of the hemostatic methods. Of note, it is emphasized that even experienced surgeons and accurate techniques cannot avoid operative ovarian reserve damage (45).

The factors that affect post-surgical decrease in the ovarian reserve continue to be a topic of debate. Overall, age at the time of surgery does not seem to be associated with the rate of AMH decline (46,47). Several studies have reported that there is a positive correlation between preoperative (baseline) AMH states and postoperative AMH decline (28,47). It is possible that a higher ovarian reserve may exhibit increased primordial follicle intensity, and in the course of the intervening process, inadvertent removal of cortex and/or surgical damage causes numerous follicles to be lost and AMH production to be significantly downregulated. It is noteworthy that although patients with high baseline AMH concentrations (high ovarian reserves) may lose a higher proportion of this reserve, they may still have a higher residual reserve than

those with low AMH levels, preoperatively (28). Likewise, bilaterality is a significant factor predicting surgery-related ovarian reserve impairment (27,48,49). Although the influence of surgery appears mitigated when only one ovary is involved, Ferrero *et al* (50) identified a higher risk of ovarian failure during surgery for recurrent unilateral endometrioma when compared with primary unilateral cases. Severity of endometrioma, based on the revised American Society for Reproductive Medicine scoring, is likely to predict the decline of post-operative serum AMH levels (51). Of note, adhesiolysis for dense and wide adhesions surrounding adnexal lesions may aggravate ovarian impairment secondary to disruption of the ovarian vascular bed, thereby postoperatively reducing blood supply (52). In terms of direct proportional correlation between cyst diameter and removed tissue during cystectomy (53), the deleterious effect is more significant following excision of larger endometriomas (54). As aforementioned, these factors may help predict ovarian reserve after operation. Of note, Wang *et al* (55) found that the decrease in the levels of AMH following cystectomy was a short-term effect, with some recovery observed within one year. Nevertheless, not every patient presented with a fully restored ovarian reserve, revealing several risk factors of permanent damage: AMH concentrations decreased noticeably after 1 year in patients with bilateral endometriomas, in individuals with cyst size >7 cm and in stage IV groups (55). In most cases, the effect of endometrioma excision on ovarian reserve is unpredictable. Time point selection for ovarian reserve testing after intervention may be critical to assessing any harmful effects. The long-term effect of surgical treatment of endometriomas on serum AMH levels requires in-depth studies.

5. Endometrioma and fertility outcomes

Endometriosis has been considered to independently cause damage over time, hereby decreasing fecundity and promoting the development of a shortened reproductive window (6). Although clinically-recognized associations have been reported, the definite cause-effect relationship between endometrima and infertility remains unclear. Surgery has long been considered the primary treatment for infertility in cases of endometrioma (36). Nevertheless, females having received cystectomy for endometrioma may experience a further reduction in ovarian reserve, prompting concern of reduced fecundity following surgery (48). Patients subject to endometrioma often pursue ART to achieve pregnancy (56,57). Several aspects associated with infertility management in an endometrioma setting remain controversial and consequences to future fertility (spontaneous and assisted pregnancy) require further clarification.

Impact of endometrioma and its excision on spontaneous conception. To date, a clear association has not been found between endometrioma and fertility. Several studies reported that the ovulation rate decreased in affected gonads, however, these were small sample studies focusing on a few ovulation cycles (58,59). Maggiore *et al* (60) investigated >1,000 menstrual cycles and reported similar ovulatory rates among affected ovaries, regardless of the size and number of endometriotic cysts. Ovulatory function can be reasonably assumed as being preserved in patients with endometrioma (60). Since endometrioma is not found to have an impact on ovulation, existing concerns have focused on its adverse effects on ovarian reserve (60). Furthermore, the ovarian reserve reveals the reproductive potential of a patient, both qualitatively and quantitatively (61). Fertility is likely to be reduced by the presence of endometrioma alone, since the association between endometriotic ovarian cysts and decreased ovarian reserve has been extensively established (25-28). However, the extent to which this impacts pregnancy in females with endometrioma is not well understood. In fact, the endometrioma usually coexists with pelvic endometriosis and it is rarely isolated; the role of endometrioma in female infertility is therefore assumed to be overestimated (62). Moreover, more than half of females with small endometriomas have pelvic adhesions and adenomyosis that could reduce fertility (62), which affects the judgment on the correlation between OMA and infertility. In a population of patients with histologically proven endometriosis, OMA showed no relation to the presence of infertility (63). Nevertheless, to further clarify this, additional research is required.

There is controversy regarding the surgical excision of endometriomas in females having received treatment for infertility. Reported pregnancy rates after laparoscopic excision of endometriomas are highly variable due to variations in patient population and length of follow-up times (60,64). Considering the multiple confounding factors and methodological drawbacks in the considered studies, the benefit of excision of OMAs is difficult to establish. While surgical OMA removal may theoretically improve spontaneous pregnancy rates by restoring the ovarian functional anatomy, some data indicated that resection of the cyst alone will not markedly affect fertility (65). Furthermore, there are concerns regarding the safety of surgery, with a reported reduction in postoperative AMH levels. Surgical excision of endometrioma may cause ovarian reserve to be reduced in a short time, which may delay achieving pregnancy (37-39). In cases of bilateral endometrioma, there is a higher risk of premature ovarian insufficiency following cystectomy (66,67). Repeated surgery for OMA has a higher risk of complications compared with primary endometrioma (68), and accumulation of postoperative adhesions over a lifetime may affect future fertility. Moreover, low AMH levels following surgery are predictive of earlier menopause and a shorter reproductive lifespan (69,70).

Impact of endometrioma and its excision on ART outcomes. When scheduling ARTs for infertile patients with endometrioma, Ferrero *et al* (71) reported a noticeably lower number of oocytes retrieved from the affected gonads compared with the contralateral ovaries. Extensive evidence suggested that the presence of OMA affected ovarian responsiveness to superovulation at the time of ART (72,73). A previous study reported that fertility results for clinical pregnancy (CPR) and delivery rate in patients with endometrioma did not differ from those found in unexposed control subjects (74). Hamdan *et al* (72) also found similar CPR rates and live birth rates (LBR) in patients with endometrioma and control subjects. This evidence suggested that endometrioma caused quantitative rather than qualitative injury to ovarian reserve. Hence, even if the number of oocytes retrieved is decreased in

Table I. Fertility outcomes after surgery and non-surgery management of endometrioma following assisted reproductive technology.

Population	Type	Design	Fertility outcomes	Author, year	(Refs.)
Subfertile women with OMA undergoing ART	Meta-analysis	10 studies with 1,354 women significant differences (OR, 1.08; 95% CI, 0.80-1.45); LBR no significant differences (OR, 0.75; 95% CI, 0.54-1.06).	CPR no	Nickkho-Amiry *et al*, 2018	(76)
Subfertile women with OMA undergoing ART	Meta-analysis	13 studies with 2,878 women significant differences (OR, 0.83; 95% CI, 0.66-1.05) LBR no significant differences (OR, 0.83; 95% CI, 0.56-1.22)	CPR no	Wu *et al*, 2018	(77)
Subfertile women with OMA undergoing ART	Sytematic review	10 studies with 1,650 women significant differences (OR, 0.87; 95% CI, 0.64-1.18)	LBR no	Brink *et al*, 2017	(80)

OMA, ovarian endometrioma; ART, assisted reproduction treatment; CPR, clinical pregnancy rate; LBR, live birth rate; OR, odds ratio; CI, confidence interval.

patients presenting with OMA, the chances of pregnancy are not affected (74,75).

When scheduling ART for infertile cases with endometrioma, clinicians should consider whether to perform prior resection for endometriotic cysts. Extensive evidence indicated that surgery for OMA may cause damage on ovarian reserve (37-39). Moreover, much evidence (76-78) suggests that surgery for OMA has an adverse effect on ovarian response, with a reported reduction of oocytes retrieved following surgery. Recently, a meta-analysis including 28 studies investigated whether pre-ART cystectomy improved fertility, and no evidence showed any benefit of surgery, instead reporting similar CPR rates and LBR between females having undergone surgery for endometriomas and those who did not (76). Additionally, evidence from other studies demonstrated that females having undergone surgery for endometrioma before *in vitro* fertilization (IVF) or intracytoplasmic sperm injection exhibited similar fertility results compared with controls (77-80). To the best of our knowledge, meta-analyses published to date did not detect any improvement in ART outcomes in patients undergoing cystectomy for OMA (Table I). Results from other data contradicted these findings and proposed that IVF outcomes were significantly impaired in females previously operated for OMA. One such investigation revealed that compared with patients with tubal factor infertility, females having received surgery for OMA exhibited a lower number of pregnancies (81). Another study reported that the CPR rate and LBR in ART cycles were lower in females with reduced ovarian reserve secondary to OMA cystectomy compared with females with idiopathic diminished ovarian reserve (82). Furthermore, Maignien *et al* (83) conducted a multivariate logistic regression analysis to identify the prognostic factors that affected pregnancy in IVF cycles and suggested that surgery for OMA was independently associated with lower pregnancy rates. Importantly, these studies (81-83) are limited as they are surgical in nature, and did not control for any confounding factors including, but not limited to postoperative duration, differing surgical procedure, surgeon's expertise, endometrioma diameter and laterality. Based on the available evidence, the European Society of Human Reproduction and Embryology guidelines concluded that cystectomy for endometrioma before ART treatment does not improve pregnancy rates (36).

6. Treatment of endometrioma for improving fertility

The association between endometrioma and infertility has been extensively reported in literature; however, the causal relationship between the two is still not identified. A previous study demonstrated a high overall spontaneous pregnancy rate, indicating that young females with endometrioma and no history of infertility can pursue natural conception before seeking ART treatment (60). An important question is whether females with endometrioma require ART. However, in our previous work, it was demonstrated that women could achieve pregnancy regardless of ART, indicating that treatment is not necessary. Nevertheless, employing ART procedures can increase pregnancy rate statistically. When scheduling ART for infertile patients with endometrioma, clinicians must carefully consider whether to perform surgical excision before ART. Extensive evidence indicated that surgery performed before ART treatment does not improve reproductive outcomes, whereas it extends the time to pregnancy and increases the risks and costs compared with conservative management (84). Surgical excision of endometrioma using any technique significantly affects ovarian reserve, particularly in cases of bilateral and recurrent endometriomas (48-50). In addition to unintentionally removing healthy ovarian tissue (85), other probable mechanisms affecting ovarian reserve consist of the effect

of bipolar electrocoagulation on parenchyma and blood supply of residual healthy ovarian tissue and surgery-related inflammatory response (47). Patients scheduled to receive ART treatments should only undergo prior surgical treatment in cases of severe pelvic pain, where malignancy cannot be excluded, or reduced accessibility of follicles, whereas it should not be offered to each patient presenting with endometrioma-related infertility (86,87). To minimize the adverse effect on the ovarian reserve, surgical treatment should be performed by a gynecologist with specific expertise in endometriosis and fertility. In cases of young females who are not yet planning to become pregnant, it would be appropriate to offer fertility preservation such as oocyte freezing, and embryo and ovarian tissue cryopreservation before surgery (88).

7. Conclusions

A previously published systematic review showed that both endometrioma and its removal may cause a decline in AMH levels (39). Meanwhile, cystectomy for endometrioma may not improve fertility outcomes in ART cycles (72). What is much less investigated in the literature, however, is the specific mechanism of how endometriotic cysts may damage the ovarian reserve prior to surgery. Given an increasing incidence among young individuals, apart from females undergoing ART, the impact of endometrioma and its operation on spontaneous pregnancy should also be investigated.

Endometrioma can decrease functional ovarian tissue based on space-occupying effects, local reactions or both (33). Thus, it is likely to adversely affect the primordial follicles that constitute the ovarian reserve and/or the pool of growing follicles that secrete AMH. Evidence is now emerging concerning the detrimental impact of endometrioma on reproduction (46). Surgical excision may increase the possibility to achieve pregnancy by restoring the anatomy of the affected ovaries in patients with endometrioma (46). However, pre-cycle surgical treatment of endometrioma does not appear to increase pregnancy rates in ART, along with a further detrimental impact on ovarian reserve (76-80). Considering the insufficient evidence favoring surgical excision before ART, cystectomy should only be suggested in specific situations, such as suspicious features, progressive symptoms and large cysts (87).

At present, more evidence is needed to address several issues that remain to be clarified. For example, a specific link between endometriotic cysts and infertility has not been revealed, the exact pathophysiology of subfertility related to endometrioma remains to be discussed, and whether surgery for endometrioma may benefit the patients who plan to be spontaneously pregnant is still unclear. Additionally, there is a need for well-designed randomized clinical trials comparing treatment regimens for patients with endometriomas in different clinical scenarios. Taken together, further research is necessary to optimize the management of females with endometrioma requiring the preservation of ovarian reserve and subsequent reproductive potential.

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Competing interests

The authors declare that they have no competing interests.

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