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Endometrioma surgery: Hit with your best shot (But know when to stop)

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ABSTRACT

Ovarian endometriomas (OEs) are commonly detected by ultrasound in individuals affected by endometriosis. Although surgery was widely regarded in the past as the gold standard for treating OEs, especially in the case of large cysts, the surgical management of OEs remains debated. Firstly, OEs often represent the "tip of the iceberg" of underlying deep endometriosis, and this should be considered when treating OEs to ameliorate patients' pain for focusing on the surgical objectives and providing better patient counseling. In the context of fertility care, OEs may have a detrimental effect on ovarian reserve through structural alterations, inflammatory responses, and oocyte reserve depletion. Conversely, the surgical approach may exacerbate the decline within the same ovarian reserve. While evidence suggests no improvement in in-vitro fertilization (IVF) outcomes following OE surgery, further studies are needed to understand the impact of OE surgery on spontaneous fertility. Therefore, optimal management of OEs is based on individual patient and fertility characteristics such as the woman's age, length of infertility, results of ovarian reserve tests, and surgical background. Among the available surgical approaches, cystectomy appears advantageous in terms of reduced recurrence rates, and traditionally, bipolar coagulation has been used to achieve hemostasis following this approach. Driven by concerns about the negative impact on ovarian reserve, alternative methods to obtain hemostasis include suturing the cyst bed, and novel methodologies such as CO_2 laser and plasma energy have emerged as viable surgical options for OEs. In instances where sonographic OE features are non-reassuring, surgery should be contemplated to obtain tissue for histological diagnosis and rule out eventual ovarian malignancy.

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1. Introduction

Endometriosis is a benign chronic and persistent disease dependent on estrogen, recognized by the presence of endometrial-like tissue outside the uterine cavity, which predominantly afflicts women during their reproductive years [1].

The precise origin and pathogenesis of endometriosis is still not fully understood, as it is characterized by a complex interaction of elements that contribute to its onset and establishment. In fact, various irregularities in the immune system, genetic predispositions, and environmental factors collectively impact a woman's susceptibility to this chronic benign disease [2]. While endometriosis can be symptomless, it typically manifests as distressing pain symptoms and/or infertility, negatively impacting the quality of life (QoL) of patients affected [3].

The exact incidence of endometriosis remains uncertain whereby a conclusive diagnosis requires surgical procedures and histological assessment. Estimates indicate that this chronic benign disorder affects at least 6–10% of women in their reproductive years [4]; however, given the significant quantity of women encountering painful symptoms and/or fertility issues, it is conceivable that the frequency of endometriosis might surpass the existing estimated rates [5]. Moreover, the actual prevalence may be underestimated due to undiagnosed cases without noticeable symptoms or investigated by operators with limited expertise at imaging or at surgery [4].

Peritoneal endometriosis, ovarian endometrioma (OE), and deep endometriosis (DE) represent the three main phenotypes of pelvic endometriosis [6]. The varied anatomical locations affected by endometriosis contribute to the wide spectrum of symptoms experienced by individuals, emphasizing the need for comprehensive assessment and personalized management strategies [4]. For example, urinary symptoms frequently arise from involvement of the bladder or ureter, while intestinal symptoms commonly result from the presence of bowel nodules [7–9]. The primary therapeutic strategy for most endometriosis-related pain cases emphasizes medical management, particularly hormonal therapies [3]; otherwise, surgical intervention is strictly necessary in some specific cases, such as in presence of ureteral stenosis, bowel occlusion, or ovarian cysts with suspected malignant features.

An OE is commonly detected in individuals affected by endometriosis. Symptoms related to OEs are usually strongly influenced by the concomitant presence of DE [10]. Accurate diagnosis of OE can often be achieved through the use of transvaginal sonography (Fig. 1) [11]. The determination of an appropriate management of OEs approach hinges on numerous clinical parameters that demand careful consideration [12]. Treatment choices encompass expectant management, medical interventions, or surgical procedures, or a combination of these approaches, specifically for cases of pain-related endometriosis [13]. Although the impact of OE on women's fertility continues to be a topic of debate and controversy [14], in vitro fertilization (IVF) has a relevant role in managing infertility related to endometriosis, and therefore, is often adopted in patients who have also OEs (Fig. 2).

In the past, surgery was widely regarded as the gold standard for treating OEs, especially in the case of large cysts [15]. However, accumulating evidence suggests a potential negative impact of excisional surgery on ovarian reserve [16,17]. Consequently, in recent years, there has been a trend toward adopting more conservative approaches for OEs, likely resulting in fewer referrals for surgery [12]. In conclusion, in current clinical discussions with patients diagnosed with OEs, gynecologists are confronted with a dilemma, having to decide between opting an expectant management, a medical therapy or a surgical intervention. In this topic, the preservation of ovarian reserve has emerged as a pivotal topic in both research and academic discourse [18]. Therefore, this review aims to assess the existing evidence regarding the management of OEs, placing particular emphasis on the question of when surgical treatment should be pursued.

2. Ovarian endometriomas: general characteristics and impact on fertility

OEs are a common manifestation of endometriosis, with their prevalence estimated to be between 17% and 44% among patients diagnosed with the condition [19]. Epidemiological research indicates a higher OE risk linked to early menarche, frequent and shorter menstrual cycles, dysmenorrhea, low body weight, tall stature, alcohol and caffeine consumption, and a family history of endometriosis. Conversely, regular exercise, higher parity, and smoking may reduce the OE risk [2]. In general, the prevalence of OE reflects that of endometriosis, with increasing evidence pointing to genetic, phenotypic, and lifestyle elements, along with environmental factors, influencing its onset and development [20].

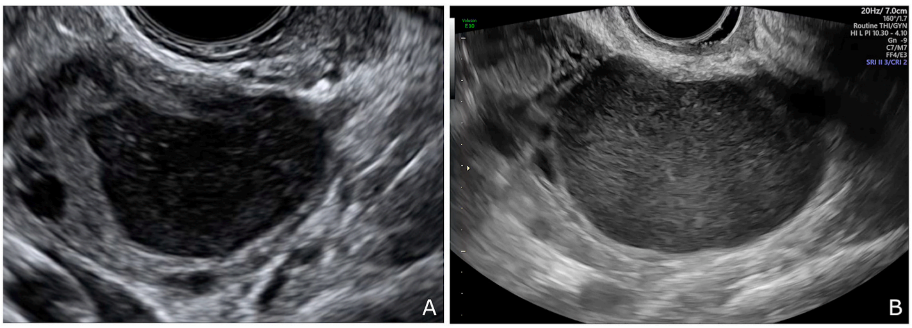

Fig. 1. Endometriomas appear at ultrasound in a premenopausal patient as an adnexal mass with ground glass echogenicity of the cyst fluid, one to four locules and no papillations with detectable blood flow (a and b). In the case of large endometriomas, the ovarian follicles appear laterally compressed by the cyst.

The pathophysiology of OE formation is complex and multifactorial, much like endometriosis itself [21]. OEs tend to occur more often on the left ovary (60%), a trend attributed to factors such as the menstrual reflux theory and anatomical distinctions between the left and right hemipelvis [22,23]. OEs typically occur unilaterally, and, when affecting both ovaries, suggest a broader extent of the condition with presence of DE and obliteration of the pouch of Douglas [24]. Prominent theories include invagination stigma, where ectopic endometrial tissues from surface implants or recent corpus luteum colonization become trapped in the ovarian cortex [25]; an alternative theory suggests that the peritoneum encasing the ovary undergoes metaplasia, transforming into endometrial tissue, which eventually gives rise to the formation of a cyst [26]. Histological examination of OEs reveals their endometriotic nature in all cases, with approximately 60% of the inner wall covered by endometriotic tissue. In nearly all instances, the depth of penetration of this tissue is less than 1.5 mm and the average cyst wall thickness range from 1.2 to 1.5 mm, prospective crucial factors to consider before electrosurgical intervention [27]. The development of this pseudocyst seems to create an inflammatory milieu beneath the ovarian cortex, resulting in dense adhesions between them, a feature not observed in other benign ovarian cysts. This explains why identifying and separating the cyst from the adjacent ovarian cortex during surgery becomes challenging [25].

The diagnosis of OEs typically relies on ultrasound findings showing a unilocular or multilocular ovarian cyst with internally homogenous low-level echogenicity ("ground-glass echogenicity") and lacking solid components or internal vascularity [11].

It has been hypothesized that OEs may impact ovarian fertility via structural alterations, inflammatory responses, and oocyte reserve depletion: first, these cysts may distort pelvic anatomy, hindering fallopian tube function; additionally, they can elevate inflammatory markers, impairing tubal and sperm motility, while free radicals further affect embryo development [28].

Histological studies examining the functional morphology of the ovarian cortex surrounding benign cysts have shown that OEs are linked to decreased follicular number and activity in comparison to teratomas or other benign cystadenomas [29]. A recent study noted that women with OEs exhibit lower levels of anti-Müllerian hormone (AMH) and antral follicle count (AFC) compared to those without these cysts. This implies that the mere presence of OEs could be linked to a decline in ovarian reserve [30]. Additional studies indicate a reduction in follicular density in ovaries affected by OEs compared to healthy ones [31]. Moreover, early follicles in ovaries affected by OEs are more prone to atresia, further diminishing ovarian reserve. Increased fibrosis and inflammation within the ovary can lead to oxidative stress and apoptosis [32]. This oxidative stress may affect oocyte quality, resulting in slower embryo development and increased arrest. Mechanical stretching on the ovarian cortex from OEs can also harm follicles [33]. This impact on ovarian reserve is particularly notable in bilateral OEs and unilateral large OEs (more than 70 mm) [34].

The impact of OEs on ovulation is controversial. As reported in a Japanese study from two decades ago, a decrease in ovulation has been observed in a small cohort of patients (n = 26) affected by OEs, particularly in cases where the OE size exceeds 4 cm [35]. Another prospective study on 70 consecutive women with monolateral OE who had not undergone previous adnexal surgery underwent serial ultrasonographic examinations to determine the side of ovulation. Ovulation occurred in the affected ovary in 22 cases (31%; 95% CI: 22–43%). Assuming that the expected rate of ovulation in both ovaries in healthy women was similar, this difference was considered statistically significant (P = 0.002) [36].

On the contrary, a previous Italian group conducted a more extensive study involving seventy women with unilateral OE, tracking ovulation over six menstrual cycles. The study revealed similar rates of ovulation between healthy and affected ovaries, with 43% of patients achieving spontaneous conception during the study period. It is important to note that these patients did not have any other known infertility risk factors. These findings provided support for a conservative approach in managing unilateral OEs in young asymptomatic women with no history of subfertility [37]. Another study found that the presence of OEs reduced crude and cumulative spontaneous pregnancy rate in patients with rectovaginal endometriosis compared with patients with rectovaginal endometriosis but without OEs, in patients treated with the use of either expectant or surgical management [38].

3. Choosing surgical candidates: key preoperative factors to consider

A critical point for reducing unintentional harm to ovarian reserve is initially based on meticulously choosing patients with OEs who need surgery. The decision to opt for surgical management of an OE must consider various factors including the patient's

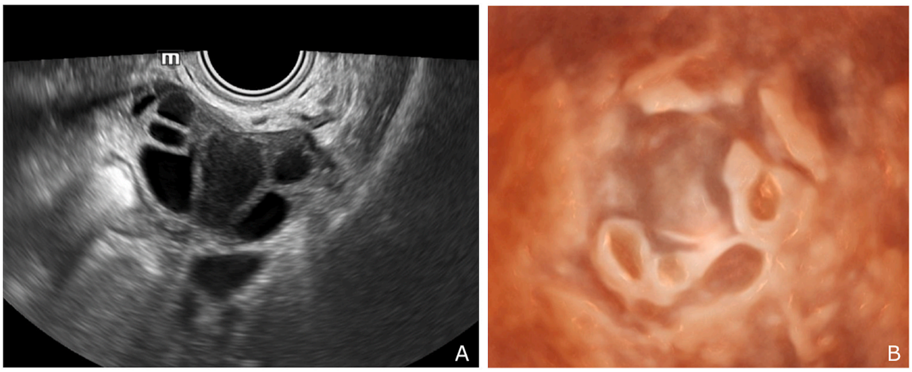

Fig. 2. A small endometriomas (a) in a patient submitted to ovarian stimulation for in vitro fertilization, with 3D reconstructions (b).

treatment objectives (addressing pain, infertility, or both), age, surgical history, disease severity, and suitability for spontaneous conception attempts [39].

Medical treatment can diminish the size of OEs; however, its primary aim is to manage symptoms and limit the progression of the underlying disease, rather than achieving a cure for the condition itself [40–42]. A recent meta-analysis has comprehensively investigated the impact of medical therapy on OE, evidencing how dienogest, oral contraceptive pills, gonadotropin-releasing hormone agonists, norethindrone acetate, and danazol have all been shown to reduce cyst diameter by a mean of 0.6–1.95 cm [43]. In general, hormonal therapies, the cornerstone of medical treatment, hinder ovulation, limiting their applicability in women seeking pregnancy. Therefore, albeit lacking a precise threshold for lesion size, medical intervention should be preferred for small or recurrent OEs, or individuals disinclined towards surgical options.

Surgery is recommended for treating patients with endometriosis when bowel nodules cause a relevant intestinal lumen stenosis and (sub)occlusive symptoms, when there is ureteral stenosis due to endometriosis leads to hydronephrosis or when OEs show ultrasound features suspected or suggestive of malignancy [12]. Alternatively, surgical intervention may be warranted when hormonal therapies, which serve as contraceptives, are deemed unsuitable for alleviating pain symptoms in infertile women with endometriosis [40,44].

The surgical excision of OEs in the context of fertility care is a topic of controversy either for spontaneous conceptions or for that obtained by IVF (see next chapters). In general, arguments supporting surgery include obtaining histological confirmation of diagnosis, addressing pelvic pain, or enabling effective oocyte retrieval, in the case of IVF. In this latter case, where difficult access to follicles during oocyte pick-up is predicted, surgical intervention may have a role in restoring normal pelvic anatomy and improving ovarian access during oocyte retrieval [45]. However, surgical treatment of OEs can lead to a decrease in ovarian reserve, likely due to the disruption of the normal ovarian cortex and potential damage during hemostasis [46].

If surgical treatment of endometriotic cysts encompasses a variety of techniques and combined approaches, preoperative counseling regarding potential ovarian reserve damage is essential. Moreover, individuals at heightened risk, such as those with advanced reproductive age, baseline diminished ovarian reserve, or bilateral OEs, may benefit from fertility preservation discussions. This could entail oocyte or embryo cryopreservation before laparoscopy, or ovarian tissue cryopreservation before or at the same time as surgery [47].

Generally, for patients not desiring fertility, oophorectomy is sometimes considered in place of cystectomy, particularly in the setting of large or recurrent cysts. Nevertheless, patients should be counseled on the risk of contralateral ovary recurrence after unilateral oophorectomy. In one study of 50 patients who underwent laparoscopic unilateral salpingo-oophorectomy for unilateral OE, the risk of recurrence on the contralateral ovary during the first 5 years after unilateral salpingo-oophorectomy was 24.7% [48].

The presence of an adnexal mass in perimenopausal women raises concerns for malignancy, especially when coupled with a history of endometriosis [25]. In instances where sonographic OE features are non-reassuring or it shows a rapid growth, surgery should be contemplated to obtain tissue for histological diagnosis and rule out ovarian malignancy. It should be also considered that, even in the absence of these concerning signs, approximately 0.9% of cases may unexpectedly reveal malignancy upon histological examination [49]. In fact, endometriosis is rarely associated with malignant transformations and degenerations, predominantly confined to the ovaries, evolving from OEs [50], particularly with endometrioid and clear cell subtypes. The specific reasons behind malignancy developing almost totally from them remain largely unknown, but have been likely attributed to the distinct microenvironment present at this site [51].

Data relate to new ovarian OEs in perimenopausal, and postmenopausal women are scarce, presenting a puzzling scenario of a condition presumed to be estrogen-dependent, challenging our comprehension of its underlying pathophysiology. In this complex scenario, as age increases, multilocular OEs or characterized by papillations and other solid components become more common, while the typical ground glass echogenicity of cyst fluid and tender mass on ultrasound scan become less common. Thus, the risk that a woman presenting with an ovarian endometrioma will undergo unnecessary surgery because of suspicion of malignancy is likely to increase with her age, also considering that both subjective assessment and published ultrasound rules for diagnosing OEs have much poorer performance in patients 40 years or older [52]. Therefore, new cases of perimenopausal and postmenopausal OEs require a more careful and vigilant monitoring and their management should be based on a shared decision with the patient after extensive counseling.

4. Surgical treatment options of ovarian endometriosis

4.1. Cystectomy

Cystectomy has historically been the preferred method for comprehensive surgical excision, supported by substantial evidence indicating symptom improvement and reduced recurrence risk compared to ablation techniques [53].

During cystectomy, a “stripping” technique is employed, wherein a plane is established between the cyst wall and the normal ovarian cortex (Fig. 3). This plane is then refined through the application of traction and countertraction using gentle, non-traumatic instruments. This task can be exceptionally challenging due to the fibrosis and inflammation commonly associated with OEs, which can hinder the identification of the correct surgical plane [54]. It has been reported that dilute vasopressin can effectively reduce bleeding and improve accessibility to the surgical plane [33], but its use is not widely employed in this setting.

Due to the inherently challenging nature of this procedure, recent concerns have emerged regarding the possibility that in certain instances, the stripping method might unintentionally result in the removal of healthy ovarian tissue, also linked to coagulation within the remaining ovary [55], resulting in a subsequent decline in ovarian reserve [17]. A recent study indicates that the reduction in ovarian reserve post-surgery does not exhibit a direct correlation with the quantity of ovarian tissue inadvertently removed alongside the OE wall during excisional surgery. This provides indirect evidence suggesting a change unrelated to the excisional technique itself [56].

Numerous studies have shown that laparoscopic OE cystectomy can result in decreased levels of AMH. A recent prospective study revealed that among patients with OEs, there is a statistically significant decrease in AMH levels following cystectomy. Furthermore, this decrease is exacerbated with an increase in cauterizations [57]. In another prospective longitudinal study, a significant decrease in serum AMH levels was noted in patients undergoing surgery for endometriosis compared to those operated on for other benign cyst types. Subsequent serial follow-ups at 7, 30, and 90 days revealed a gradual improvement in AMH levels, eventually reaching an impressive recovery rate of 65% [58]. Furthermore, in 2015 a prospective study provides evidence that AMH tend to recover by approximately 12 months postoperatively [59]. It has been hypothesized that this recovery may be attributed to surgery impacting recruited follicles rather than healthy primordial tissue, which could potentially lie deeper beneath the surface of the ovarian cortex. However, the authors stress the need for future adequately designed randomized controlled trials (RCTs) to further investigate this phenomenon. A comprehensive meta-analysis revealed a statistically significant decline in AMH levels postoperatively, with a reduction of 1.13 ng/mL compared to preoperative levels, indicating a substantial decrease of 38%. Importantly, the impact varied between unilateral and bilateral cystectomy, with serum AMH decreasing by 30% and 44%, respectively [60]. Throughout ovarian surgery, multiple mechanisms may contribute to impairment of ovarian reserve, such as the mechanical extraction of healthy ovarian cortex, coagulation of residual ovarian tissue post-excision, and the inflammation and edema induced by the surgical procedure [61, 62].

During cystectomy, the hemostatic strategy may impact ovarian reserve. Traditionally bipolar coagulation has been used to achieve hemostasis following removal of the OE. In addition to inadvertent removal of follicles adjacent to the endometriotic cyst wall, cauterization of the cyst bed near the ovarian hilus has been hypothesized to disrupt ovarian circulation and cause to further loss of follicles. Alternative methods to obtain hemostasis include suturing the cyst bed, application of a hemostatic sealant or gauze packing [54,63,64]. A 2015 meta-analysis aimed to evaluate the effect of suture versus bipolar coagulation on ovarian reserve concluding that while AMH decreased significantly in both groups, the decrease was more pronounced with bipolar coagulation compared to suture [65]. Another past decade meta-analysis compared bipolar coagulation with suturing and the application of a hemostatic agent [66]. The study revealed that hemostatic agents led to a significantly lesser decline in AMH at three months compared to bipolar coagulation, while no difference was found between hemostatic agents and sutures. Despite hemostatic agents being non-inferior to sutures in terms of AMH decline and achieving hemostasis, their use should be cautioned due to cost considerations and the potential risk of allergic reactions. They noted that allergic reactions to the hemostatic agent (which consisted of a combination of bovine gelatin matrix and thrombin powder) could result in eosinophilic granulation, which may increase adhesions and the likelihood of small bowel

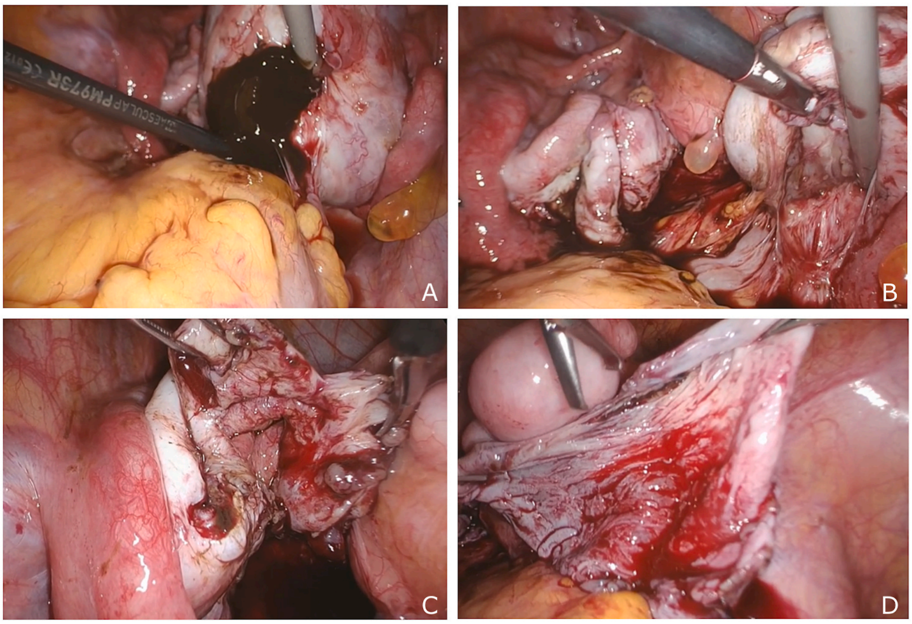

Fig. 3. The ovary with the endometrioma is mobilized from its adhesion to the ovarian fossa, and after cyst rupture, which invariably occurs at the site of adhesion, the cyst content is repeatedly rinsed (a). After mobilization, the site of initial adhesion and cyst rupture is completely exposed (b). Therefore, the cyst wall is stripped starting from the original adhesion site, where the ovarian parenchyma and the endometrioma are thin and densely adherent to each other. After identifying the cleavage plane using either technique, the stripping procedure is then continued for the remaining part of the cyst wall in the conventional manner by exerting traction in opposite directions with two atraumatic grasping forceps (c and d). At the end of cyst wall excision, regardless of the technique used, additional hemostasis is obtained, if necessary, with bipolar forceps applied to the ovarian parenchyma.

obstruction, although the available data for this were limited to a few of case reports [67]. In a recent meta-analysis, the efficacy of sutures, bipolar coagulation, ultrasonic coagulation, and hemostatic matrix during cystectomy was examined. The findings revealed a decrease in AMH at 3 months for all hemostasis methods, albeit varying in magnitude among the different techniques. Bipolar coagulation induced the most significant decrease, followed by ultrasonic coagulation and hemostatic matrix. Suturing caused the least damage to AMH, in particular, if barbed suture was employed [68].

A variation of cystectomy involves a "three-step" approach. In the initial surgery, the OE is fenestrated, and the inner fluid is aspirated. Subsequently, the cyst wall is irrigated, and additional lysis of adhesions and restoration of anatomy are carried out. Following the initial surgery, the patient undergoes medical therapy for 12 weeks postoperatively and then returns for a second surgery. During this second surgery, further lysis of adhesions is conducted, along with either cystectomy or laser ablation of the cyst wall [69]. In line with this, a small RCT provides reassurance that under certain circumstances, AMH can recover. In this study, patients were randomly assigned to either the three-step therapy or traditional cystectomy group. AMH levels were assessed preoperatively, at 3–6 and at 9–12 months, postoperatively. Both groups exhibited a significant decrease in serum AMH at 3–6 months. However, the three-step approach group demonstrated improvement in AMH levels to near baseline at 12 months, whereas the traditional cystectomy approach did not show improvement in AMH levels [70].

4.2. Ablation

Traditionally, the cyst wall ablation can be achieved through three methods: electrosurgical energy (monopolar or bipolar), laser ablation, and plasma energy. This approach typically involves three steps: fenestration, aspiration, and irrigation of the cyst. Nevertheless, ablation achieved through CO2 laser or plasma energy may induces less thermal injury to the ovary compared to ablation performed with monopolar or bipolar electrosurgery [71]. However, it remains unclear whether the advantage of preserving ovarian reserve with ablation via plasma energy translates into improved fertility outcomes.

CO_2 laser ablation has been investigated as an alternative to the thermal spread associated with electrosurgery. However, in this technique, the cyst wall is externalized and treated with a CO_2 laser [72]. In a small prospective trial, laser ablation was performed on OEs, showing increased AFC in unilateral cases only compared to preoperative levels, while AMH remained unchanged. No significant changes in AFC or AMH were observed in bilateral cases. The limitations of this trial included small sample size and exclusion of patients with DE. Mean OE size was approximately 40 mm, thus, limiting the study of patients with larger cysts.

In an Italian RCT [73], AMH levels were analyzed both before and after surgery in 48 were randomly assigned to electrosurgery ablation and cystectomy for OEs. Postoperatively, there was no significant difference in AMH levels between the groups for OEs smaller than 50 mm. However, for OEs larger than 50 mm, the ablation group exhibited significantly higher AMH levels compared to the cystectomy group. The authors inferred that this discrepancy could have been probably attributed to a lower risk of healthy ovarian cortex removal during cystectomy for the smallest OEs. They posit that, during ablation, the depth of necrosis marginally surpasses the thickness of the fibrous membrane surrounding the endometrial epithelium, regardless of OE size. Consequently, ablation results in a consistent level of damage to AMH regardless of OE size, whereas cystectomy's impact on AMH becomes increasingly detrimental as the cyst has a greater size [73]. In another RCT conducted in 2011, AFC was compared preoperatively and at 6 months postoperatively in patients undergoing surgery for fertility affected by bilateral OEs. One ovary underwent cystectomy, while the contralateral ovary underwent fenestration and ablation with bipolar energy. The study included 48 participants, and all surgeries were performed by the same surgeon. Ovaries treated with ablation exhibited a significantly higher AFC than those treated with cystectomy, although both showed a significantly decreased AFC compared to preoperative values. Additionally, thirty-seven patients in the study underwent IVF cycles using the same long agonist protocol, and the researchers noted that the ovary treated with cystectomy had a significantly lower number of dominant follicles, smaller ovarian volume, and fewer retrieved oocytes compared to the ovary treated with ablation [74].

A recent meta-analysis examined AFC and AMH levels pre- and post-operatively for cystectomy and ablation. The findings revealed no significant difference in postoperative AMH levels between cystectomy and ablation groups; however, there was a significantly higher AFC observed in the ablation groups [17]. Furthermore, another recently published meta-analysis comparing CO2 laser ablation to cystectomy revealed that laser ablation led to a notably smaller decrease in AMH and higher AFCs. No significant differences were found in postoperative pregnancy rates or recurrence rates, albeit showing a limitation in the lack of long-term follow-up for patients in the included studies [75].

Argon plasma, a substitute for CO_2 laser or electrosurgery, has been in use since roughly 2000s, to induce tissue necrosis, resulting in substantially reduced thermal dispersion. In 2010, a pilot study investigated the histology of 10 ovarian OEs treated with plasma vaporization and subsequently excised via cystectomy. Merely 10% of the ovarian parenchyma excised during cystectomy showed the effects of plasma energy. This indicates that the extent of necrosis spread during cyst wall treatment is not substantial enough to impact the inner ovarian cortex during surgery [76]. In a subsequent prospective study, 22 patients with unilateral OEs larger than 3 cm underwent plasma energy ablation. Although postoperative AMH decreased by an average of one point at 3 months, this difference vanished during a follow-up assessment 7 months to 2.5 years, postoperatively, indicating AMH recovery [77]. A review of the same research group compared plasma energy ablation versus cystectomy for treating OEs. Cystectomy patients exhibited significantly reduced AFC and ovarian volume postoperatively compared to plasma ablation recipients [78].

4.3. Sclerotherapy

An alternative to cystectomy is chemical ablation using ethanol sclerotherapy. While ethanol sclerotherapy has been long employed in other surgical disciplines, its application in treating OEs was initially reported in 1988 [79]. Initially, the method entailed transvaginal or transabdominal aspiration followed by sclerotherapy, but this approach posed various risks, such as infection, bleeding, inflammation, and the formation of pelvic adhesions [80].

Some Italian authors described first a laparoscopic method for ethanol sclerotherapy [81]. Initially, the cyst is drained and rinsed by making a 5-mm puncture with a monopolar coagulator, followed by irrigation and suction using a central system. Following the clear outflow of fluid, an 8-Fr Nelaton Foley catheter seals the puncture site to prevent leakage. The catheter, filled with saline, is placed at the puncture site after insertion. The cyst is then filled with methylene blue solution to check for leaks. If no leaks are detected, 95% ethanol mixed with methylene blue is introduced for 15 min. Additionally, the pelvic cavity is filled with Ringer's lactate solution to protect neighboring organs from potential ethanol spillage.

A single-center retrospective study assessed the laparoscopic ethanol sclerotherapy in 53 women with OEs characterized by largest diameter included between 4 and 10 cm [81]. Postoperative continuous hormone therapy was administered to all the patients, with discontinuation after at least 3 months for fertility or due to adverse effects. Recurrence was observed in 5 patients (9%), with smaller average cyst size upon recurrence (mean follow-up: 31 months). Of the 28 women desiring pregnancy, 16 (57%) conceived, 14 spontaneously and 2 via in vitro fertilization. No major operative complications occurred [81]. This study did not assess ethanol sclerotherapy's impact on ovarian reserve.

However, various studies investigating sclerotherapy before IVF stimulation found no difference in AFC, retrieved oocytes, embryo quality, or hormone levels compared to infertile females without ovarian cysts [82–84]. A French research group recently outlined laparoscopic ethanol sclerotherapy, detailing a 10-step procedure [85]. Similar to ablation, it entails puncturing the OE, aspirating its contents, and irrigating it. The cyst cavity is filled with a 96% alcohol solution, left for 10–15 min while the surgeon attends to other tasks, and then drained. Finally, the surgeon irrigates the peritoneum and removes any remaining cyst parts. Crucially, if the cyst ruptures before aspiration, sclerosis becomes unfeasible for the surgeon [86].

A comparable technique was recently introduced by Miquel et al. yet their team opted for a transvaginal approach, significantly enhancing cost-effectiveness [87]. Ethanol sclerotherapy is believed to induce inflammation and fibrosis in the cyst wall. A 2017 meta-analysis of OE treatment revealed two studies examining ovarian reserve post-sclerotherapy. They reported increased AFC and no AMH decline. Both studies utilized transvaginal ethanol sclerotherapy [88].

In a 2023 retrospective study, AMH and AFC were assessed pre- and post-laparoscopic ethanol sclerotherapy. After surgery, AMH notably decreased (average decrease of 1.3 ng/mL), while AFC showed no statistical difference. However, due to cost constraints, only 59% of patients underwent postoperative AMH testing, limiting the study's scope [89]. In a recent RCT, 70 patients underwent either transvaginal sclerotherapy or laparoscopic cystectomy. At 12 months, cystectomy led to a notable AMH decline, while sclerotherapy showed no significant changes in AMH levels. At the same follow-up time, recurrence rates were similar between the two groups [90].

4.4. *Cyst drainage*

Cyst drainage, involving the insertion of a needle into the cyst wall to aspirate its contents, is technically the simplest and least invasive initial removal method. This procedure can be performed laparoscopically or transvaginally under ultrasound guidance. However, OE recurrence rates have been reported to be as high as 80%–100% [91].

5. Impact of surgery for endometriomas on fertility

No large studies compared fertility outcomes after surgery for OEs in comparison with expectant management, nor studies, exploring the indication for surgery depending on the size of the cyst. Additionally, the impact of OE per se on fertility outcomes is not completely clear. An Italian study reported that the long-term spontaneous pregnancy rate in patients with OEs before and after surgical treatment is similar and inferior to that of healthy patients, suggesting a compromised reproductive performance in women with OEs [92].

A Cochrane review with meta-analysis including two RCTs found that cystectomy of OEs larger than 3 cm significantly increased spontaneous pregnancy rates compared to ablation (OR 5.21, 95% CI 2.04 to 13.29) [53]. In a meta-analysis of seven RCTs, cystectomy was associated with higher postoperative conception rates compared to fenestration/coagulation, but not compared to laser vaporization. Additionally, cystectomy resulted in lower recurrence rates of OEs compared to the other two approaches [93]. A multi-centric, prospective, case–control study evaluated the postoperative pregnancy probability between women with OMA managed by cystectomy versus plasma energy. At 24 and 36 months postoperatively, the pregnancy probabilities were 61.3% (95% CI 48.2–74.4%) versus 69.3% (95% CI 54.5–83%) and 84.4% (95% CI 72–93.4%) versus 78.3% (95% CI 63.8–90%), respectively, for plasma energy vaporization and cystectomy. Both surgical approaches yielded comparable pregnancy rates, and the analysis indicated that the type of surgical procedure did not have a statistically significant impact on the probability of pregnancy [72]. A retrospective, three-arm study compared postoperative pregnancy rates in patients with OEs undergoing cystectomy, ablation by plasma energy, or simple drainage. The overall postoperative pregnancy rate was 60.3%, with the probability of pregnancy at 12 months being 27% for cystectomy, 32% for plasma energy, and 16% for drainage. This study found a statistically significant difference in pregnancy rates between the groups ($p = 0.015$). The proportion of spontaneous conceptions was 58% for cystectomy, 43% for plasma energy, and 27% for simple drainage [94].

The evidence supporting surgical management of OEs in the context of assisted reproductive technology (ART) is limited. Although removing OEs before IVF may improve oocyte retrieval and prevent complications, neither cystectomy nor aspiration has shown to enhance pregnancy outcomes [95]. Numerous meta-analyses have scrutinized the fertility of women with OEs opting for surgery ahead of IVF versus IVF as a standalone procedure. A notable meta-analysis dating back to 2015 delved into 33 studies, encompassing three

RCTs. The findings did not reveal any variance in either live birth rate or clinical pregnancy rate among women with surgically managed versus untreated OEs undergoing IVF/ICSI [96]. Women with OEs undergoing IVF/ICSI experienced higher cancellation rates but achieved similar reproductive outcomes compared to those without endometriosis. Additionally, patients with surgically treated OEs before IVF/ICSI showed similar reproductive outcomes in terms of live birth rate (OR 0.90; 95% CI [0.63, 1.28]), clinical pregnancy rate (OR 0.90; 95% CI [0.63, 1.28]), and the mean number of oocytes retrieved (SMD 20.17; 95% CI [20.38, 0.05]) compared to women with untreated OEs [97]. Another systematic review and meta-analysis corroborated these findings by comparing the effects of surgical versus expectant management of OEs on IVF outcomes. Thirteen studies, including one RCT and twelve observational studies, were pooled for analysis. The results showed similar live birth rates in both the surgically and expectantly managed groups. Additionally, clinical pregnancy rates, the number of mature oocytes retrieved, and miscarriage rates did not exhibit statistically significant differences between the study groups. However, the total number of oocytes retrieved was lower in the surgery group [98].

6. Impact of surgery on endometrioma recurrence

Assessing these surgical methods, it is essential to examine the long-term consequence related to surgery for OEs, especially concerning recurrence, that poses a challenging clinical issue encountered frequently. Reported rates of OE recurrence after surgical intervention is estimated to be in the range of 16%–50% [99].

In a recent study, patients who had undergone either cystectomy or laser ablation for OEs were followed up for three years post-surgery. The study found that the recurrence rate was 6.3% for those who had cystectomy and 4.9% for those who underwent laser ablation. However, this difference was not statistically significant [100]. A RCT conducted in 2011 revealed a statistically significant rise in recurrence rates within the laser ablation group compared to the cystectomy group at the 12-month follow-up. However, this discrepancy seemed to be minimized by the 60-month follow-up when both groups were not undergoing postoperative hormonal suppression [101]. In a 2008 Cochrane review, recurrence rates between laparoscopic cystectomy and cyst ablation were compared, drawing from two RCTs. The analysis revealed higher recurrence rates associated with cyst ablation compared to cystectomy. However, it is crucial to note that in both studies, cyst ablation was conducted using electrosurgery, not laser or plasma energy techniques [53]. A 2013 meta-analysis compared cystectomy, cyst fenestration with electrosurgery ablation, and laser ablation for OEs. Cystectomy had lower recurrence rates than electrosurgery ablation (RR 0.5) or laser ablation (RR 0.33) [93].

Research on plasma energy has also examined OEs recurrence. In a retrospective French study, recurrence was examined in 55 patients treated for OE with plasma energy. For those without continuous postoperative medical treatment, the recurrence rate was 14.7%, while for the entire group, it was 10.9% [102]. In a meta-analysis encompassing various forms of sclerotherapy, including ethanol, methotrexate, and tetracycline, OE recurrence rates ranged from 0% to 62%, depending on the method and duration of instillation. Notably, procedures lasting over 10 min showed a lower recurrence rate (9.1%) compared to those under 10 min (62%) [88]. In conclusion, the comparative analysis between cystectomy, ablation and sclerotherapy regarding recurrence rates is limited, underscoring the necessity for RCTs to address this gap in knowledge [54].

When treating recurrent OEs, practitioners must be equipped to advise on the merits of repeat surgery versus medical management, considering the risks and benefits. While some experts argue that OEs larger than 3 cm do not typically respond to medical treatment [103], there is a shift toward conservative management, prioritizing severe refractory pain over size as the criterion for further surgery [104]. Repeated surgical interventions are associated with a more pronounced negative impact on ovarian reserve and are potentially more damaging to healthy ovarian tissue than the initial surgery [105]. Patients prioritizing fertility preservation should understand that surgery poses a heightened risk of premature ovarian insufficiency, particularly in cases of bilateral disease [106]. Moreover, the reproductive advantages of repeated surgery for recurrent OEs seem to decline with each subsequent procedure, with individuals having roughly half the likelihood of conception after secondary surgery compared to those undergoing initial surgery [107]. Indications for repeat surgery include persistent pain symptoms, suspicious imaging findings for malignancy, or a desire for fertility preservation despite a large OE. If a second surgery is necessary, employing fertility-preserving techniques to minimize ovarian damage is advised. Additionally, controlled ovarian hyperstimulation for oocyte or embryo cryopreservation may be considered before repeat surgery in women aiming for future childbearing and facing repetitive surgical interventions [33].

7. Impact of operator expertise on surgical outcomes

Surgically managing patients with OEs demands proficiency, skill, and specialized practitioners. As already evidence, current literature lacks consistency regarding how patient age and cyst size affect the decline of AMH levels after surgery for OEs. Nevertheless, key factors influencing ovarian reserve decline post-surgery did not only include surgical technique and the chosen hemostatic method, characteristics (size and laterality) of OEs, or preoperative AMH levels, but also surgeon expertise [18].

Limited research exists on how a surgeon's expertise affects the ovarian structure following laparoscopic excision of OEs. In a multicenter, prospective trial involving 50 patients, researchers assessed OE cyst wall specimens post laparoscopic excision. They measured the mean thickness of the cyst wall and inadvertently removed ovarian tissue. Comparison between experienced surgeons from four centers of excellence and residents revealed that residents' excised specimens contained thicker ovarian tissue (0.49 ± 0.30 mm vs. 0.97 ± 0.29 mm), indicating greater removal of healthy cortex by less experienced surgeons [108]. Moreover, a retrospective analysis suggests enhanced live birth rates following cystectomy conducted by an experienced surgeon versus a trainee. This study involved 149 IVF-ICSI cycles with infertile patients who had prior laparoscopic conservative treatment for ovarian OEs. There were 76 cycles with an inexperienced surgeon and 73 cycles with an experienced surgeon. Outcomes differed between cycles performed by inexperienced versus experienced surgeons. The inexperienced group exhibited lower AFC (7.5 ± 3.8 vs. 9.6 ± 6.6) and live birth rate per cycle (9.3% vs. 32.9%) compared to the experienced group, while other parameters like oocyte count, fertilization rate, embryo transfer metrics, implantation rate, and clinical pregnancy were similar between both groups. These findings highlight the potential for skilled endometriosis surgeons to reduce the loss of healthy ovarian tissue. However, in this study the impact on ovarian reserve remains uncertain due to the absence of serum AMH measurement [109]. Although further research and trials are necessary, it can be deduced preliminarily that an experienced surgeon is likely better equipped to execute the meticulous technique necessary for OE removal while preserving normal ovarian architecture [47].

8. Discussion

The management of OEs continues to spark debate within the field of reproductive medicine, as the choice of their management is guided by multiple factors [110].

The primary emphasis should be on the management of individuals presenting with OEs who desire to preserve and enhance their prospects of pregnancy, either at the time of initial presentation or at some point in the future. Based on the unique characteristics of the individual patient and fertility concomitant characteristics such as the woman's age, length of infertility, results of ovarian reserve tests, surgical background (especially prior ovarian surgery), and partner parameters (such semen analysis), adopting an initially conservative strategy for managing an OE may be considered reasonable [111].

According to the 2022 guidelines from the European Society of Human Reproduction and Embryology (ESHRE), in the first instance surgical intervention is not recommended for women who coincidentally detect an OE [12]. On the other hand, hormonal medical treatments, such as oral contraceptives, progestins, can provide relief for dysmenorrhea and pain, as they should be considered a suitable first-line option in this setting [40,112]. However, these treatments are not indicated for women who desire of childhood due to their interference on ovulation and endometrial function. Therefore, these medications are not suitable in women actively trying to conceive, except in specific cases where symptomatic women are awaiting IVF or surgical treatment [14].

OE may have a detrimental effect on ovarian reserve [30,113]; on the other hand, the surgical management of OEs may exacerbate the decline in ovarian reserve, raising concerns about its impact on fertility potential and associated reproductive outcomes. With these two assumptions it is easy to understand that the role of surgery in the management of OEs is multifaceted and requires careful consideration.

As it is rarely isolate [10], an ovarian OE found at preoperative evaluation, should inform about a higher risk of obliteration of the pouch of Douglas and DE involving the bowel. Consequently, identifying an OE on preoperative TVS may serve as an indicator of complex endometriotic disease, akin to "the tip of the iceberg." This underscores the necessity for the involvement of an experienced laparoscopic surgeon and the likelihood of longer surgical durations (Video 1) [114]. In fact, compared to cystectomy for benign neoplasms, these operations exhibit higher rates of adverse events, including readmission and conversion to laparotomy, necessitating meticulous surgical planning and postoperative monitoring to ensure optimal outcomes [115], likely due to the concomitant procedures needed for treating DE.

Supplementary video related to this article can be found at doi: 10.1016/j.bpobgyn.2024.102528

As previously described, surgical intervention may be necessary for women with endometriosis in specific situations, such as when bowel nodules result in intestinal stenosis and obstructive symptoms, when endometriosis nodules causes ureteral stenosis leading to hydronephrosis, or when OEs exhibit ultrasound characteristics suggestive of malignancy [12]. It could be reasonable to approach concomitant OEs found in all these situations, particularly when they are larger than 3–4 cm. Contrarily, the indications for surgery in infertile women with OEs remain unclear and lack well-defined guidelines [54].

Regarding surgical techniques for OEs, ongoing RCTs aim to pinpoint approaches that are more conservative in terms of preserving ovarian tissue. The goal is to identify methods that are more considerate of ovarian reserve, ensuring a more respectful approach to this aspect of the procedure [116–118]. Of the available surgical approaches, cystectomy appears advantageous in terms of reduced recurrence rates, as evidence in previous analysis [53]. Novel methodologies such as CO2 laser and plasma energy emerged as viable alternatives to cystectomy, propelled by mounting apprehensions regarding the negative impact on ovarian reserve, particularly notable in cases involving larger and bilateral OEs [119]. Ablation techniques seem to offer comparable symptomatic relief to patients while exerting a lesser impact on subsequent fertility prospects compared to more invasive surgical interventions. Ethanol sclerotherapy offers both a laparoscopic and a transvaginal approach, yet its impact on ovarian reserve remains debated [85,88]. Additionally, the chosen hemostatic strategy can affect ovarian reserve during the surgical approach for OE (particularly cystectomy). Although this topic is controversial, it has been postulated that bipolar coagulation may inadvertently remove follicles adjacent to the endometriotic cyst wall, and cauterization near the ovarian hilus is thought to disrupt ovarian circulation, leading to further follicle loss. Therefore, alternative methods for achieving hemostasis, such as suturing the cyst bed or applying a hemostatic sealant, have been investigated and seem to offer some advantages [68].

Nevertheless, comparing recurrence rates across different series poses challenges due to the variable use of hormonal contraceptives postoperatively among patients. Concerning this point, an RCT comparing patients undergoing OE cystectomy followed by continuous oral contraceptive pill intake, cyclic oral contraceptive pill intake, and no hormonal treatment showed a significant 3.5-fold reduction in postoperative OE recurrence with amenorrhea [99]. It is worth noting that 29% of women who underwent complete excision of OE without postoperative hormonal treatment experienced recurrent OE within 24 months post-surgery, supporting the fact that, the ovary, as a site of high disease localization, exhibits notable postoperative recurrence rates, particularly in normo-ovulatory patients [119]. In general, we deem that the choice of performing cystectomy, vaporization, or ablation (with CO2 laser, plasma jet, or radiofrequency) is also guided by surgeon expertise, and all techniques may not be widely available. Importantly, it should be remembered that repeated surgical excision of recurrent OE poses challenges, as it has been shown to negatively impact ovarian reserve and increase the likelihood of recurrence [105,120].

It has been reported that surgical management of OEs, particularly when a cystectomy is performed, may improve the chances of spontaneous conception [53]. Nevertheless, we deem that this topic is very controversial, and influenced by different bias characterizing the studies published in the current literature. Importantly, it should be noted that OEs are often not present in isolation [10], and the presence of concomitant DE may further negatively impact fertility. In our opinion, to better understand the impact of OEs per se on fertility, new studies are needed that compare patients with isolated OEs (less of 25–30% of cases) who undergo surgery versus those managed expectantly, with the exclusion of at least concomitant large DE confirmed by skilled ultrasound following the IDEA criteria [121] proposed only in the last ten years. Also in this case, it should be considered the reliability of data due to the possible impact of the presence of superficial endometriosis that need yet a surgical certain diagnosis and it cannot diagnosed with high accuracy on ultrasound [122].

Lastly, there is no discernible difference observed in terms of the number of embryos available for transfer or the clinical pregnancy rate in patients who underwent OE excision prior to IVF, as compared to those who did not undergo surgery. These findings have been consistently supported by significant meta-analyses, further confirming that surgical treatment of OEs does not lead to improved outcomes in IVF [123,124]. Also in this case, it not easy to understand the impact of underlying DE present in the cohort of patients with OEs submitted to IVF, who could have been not submitted to a skilled ultrasonographic exclusion of concomitant deep disease. To answer to both fertility topics, new conclusive data will be hopefully published in the next years, also considering the growing improvement in the non-invasive diagnosis of endometriosis.

9. Conclusion

The management of OEs encompasses various strategies, including expectant management, medical therapy, or conservative surgery aimed at preserving healthy ovarian tissue. In the complex scenario related to when and how surgically treating OEs, additional RCTs are imperative to identify the optimal approach in order to minimize the risk and incidence of recurrence while simultaneously improving long-term fertility outcomes for patients. Individualizing treatment and selecting the most appropriate surgical approach for each patient is paramount, also recognizing that surgical outcomes can significantly vary based on the surgeon's expertise and the healthcare facility's capabilities.

10. Practice points

- A critical point for reducing unintentional harm to ovarian reserve is meticulously selecting patients with ovarian endometriomas (OEs) who necessitate surgery. The decision to opt for surgical management of an OE must consider various factors, including the patient's treatment objectives (addressing pain, infertility, or both), age, surgical history, disease severity, and suitability for spontaneous conception attempts.
- In general, hormonal therapies, a cornerstone of medical treatment, hinder ovulation, limiting their efficacy in women seeking pregnancy. Therefore, despite lacking a precise threshold for lesion size, medical intervention should be preferred for small or recurrent OEs or individuals disinclined towards surgical options.
- Surgery is mandatory when OEs show ultrasound features suspected or suggestive of malignancy or when hormonal therapies, which serve as contraceptives, are unsuitable for alleviating pain symptoms in infertile women with endometriosis.
- The surgical excision of OEs in the context of fertility care is controversial for both spontaneous conceptions and in-vitro fertilization (IVF). Arguments supporting surgery include obtaining histological confirmation of diagnosis, addressing pelvic pain, or enabling effective oocyte retrieval in IVF. On the other hand, surgical treatment of OEs can decrease ovarian reserve due to the disruption of the normal ovarian cortex and potential damage during hemostasis.

11. Future agenda

- Regarding surgical techniques for ovarian endometriomas (OEs), randomized controlled trials (RCTs) are requested to pinpoint approaches that are more conservative in preserving ovarian tissue. The goal is to identify methods that are more considerate of ovarian reserve, ensuring a more respectful approach to this aspect of the procedure.
- It has been reported that surgical management of OEs, particularly when a cystectomy is performed, may improve the chances of spontaneous conception. Nevertheless, this topic is very controversial and influenced by various biases in the studies published in the current literature. Data on spontaneous fertility comparing surgery and expectant management in patients with OEs are demanding.
- New studies comparing recurrence rates after surgical treatment of OEs are needed, particularly considering the heterogeneous use of hormonal therapies postoperatively characterizing the studies published in the current literature.
- In the complex scenario of when and how to surgically treat OEs, additional RCTs are imperative to identify the optimal approach to minimize the risk and incidence of recurrence while simultaneously improving long-term fertility outcomes for patients.

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CRediT authorship contribution statement

Umberto Perrone: Writing – original draft, Investigation. **Simone Ferrero:** Writing – review & editing, Supervision. **Irene Gazzo:** Methodology. **Alberto Izzotti:** Resources, Project administration. **Umberto Leone Roberti Maggiore:** Formal analysis, Data curation. **Claudio Gustavino:** Visualization, Supervision. **Marcello Ceccaroni:** Writing – review & editing. **Stefano Bogliolo:** Validation, Supervision. **Fabio Barra:** Writing – original draft, Conceptualization.

Declaration of competing interest

The authors did not have conflict of interest to declare.

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Appendix A. Supplementary data

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