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Commentary

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Women's Health

Fertility preservation in women with ovarian endometriosis

"With advanced technology and changed patient demands in the recent years, now a concept has emerged in context of surgery playing a crucial part in enhancing in vitro fertilization outcome and fertility preservation."

Keywords: assisted reproductive technologies • cryopreservation • cystectomy • endometrioma • endometriosis • fertility • fertility preservation • infertility • ovarian • ovarian reserve • surgical methods



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Endometriosis can be encountered in 20% of women in reproductive ages and may cause infertility, dysmenorrhea as well as chronic pelvic pain. Endometriomas could be seen in 17–44% of women with endometriosis and they are most commonly observed in women with advanced endometriosis [1]. There are some studies indicating a compromised ovarian reserve in case of a space occupying endometrioma. The presence of an endometrioma correlates with a lower number of developing follicles, lower number of retrieved oocytes, a lower embryo quality and implantation rate during an *in vitro* fertilization cycle, although pregnancy success does not seem to be affected [2,3].

Even though there are certain medical treatment modalities for patients with endometriosis, patients resistant to medical treatment or those having an endometrioma may require surgery. Standard surgical approach is the excision of the endometrioma cyst wall as a whole. However, there is a potential that any surgical trauma to the ovary may compromise ovarian reserve. The implicated causes of ovarian damage during endometrioma surgery includes mechanical injury that is associated with the removal of adjacent healthy ovarian tissue along with the cyst wall and thermal damage generated by energy modalities used during hemostasis following cyst removal [4–6]. This may result in reduced ovarian response during ovarian stimulation and premature ovarian failure. Bilateral endometriomas, presence of multiple endometriotic cycts and recurrent ovarian surgery increases the risk of ovarian failure. A recent study showed that in women previously submitted to surgery for endometriosis, the mean age at menopause is significantly lower compared with a reference population [7]. Furthermore, the onset of menopause appears to be even earlier in patients who underwent surgery for bilateral endometriomas. Moving the onset of menopause to an earlier age was reported in three out of 126 women following surgery for bilateral endometriomas in a different study [8].

Various procedures were suggested to minimize ovarian damage associated with ovarian surgery. Suturing the ovarian cortex rather than electrosurgical coagulation, electrosurgical ablation of the cyst wall after drainage of the cyst contents, conserving the cyst wall adjacent to ovarian hilus during cystectomy and utilization of some novel hemostatic agents following stripping of the cyst wall are among the alternatives. Despite these, it is well established that there is a reduction in ovarian reserve in comparison to preoperative status following any type of endometrioma surgery. Thereby, there is need that novel strategies should be developed to preserve fertility in patients having endometriosis, especially in the case of endometrioma. In this article, all available fertility preservation options using assisted reproduction and cryopreservation technologies as well as less invasive surgical techniques will be discussed in detail.

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Endometriosis, ovarian reserve & fertility

The current evidence supports a dual compromising impact on ovarian reserve caused by endometriomas – an inherent injury to healthy ovarian tissue related to endometriomas and a further effect associated with surgery. Follicular depletion in the ovaries has been related to oxidative stress that occurs in women with endometriomas [9–11]. It has also been confirmed that the oxidative stress can induce necrosis in early follicles and apoptosis of the oocytes *in vitro* [10].

The major problem in surgical treatment of endometriomas is potential damage to ovaries. In theory, it is possible that among the follicle stockpile, actively growing follicles are those that are most likely to be damaged by electrocoagulation or mechanical dissection as compared with nondividing quiescent primordial follicles [4]. The possible compromise in ovarian microvasculature may have a further detrimental effect on the growing follicles. Furthermore, it is not known whether consecutive temperature increase in 'healthy' ovarian portions that is caused by electrocoagulation is detrimental to all growing follicles in the coagulated ovary [12].

It is well known that ovarian reserve is made of primordial follicles embedded in the outer 1-mm layer of the ovarian cortex [13]. Histologic studies have consistently demonstrated that some ovarian tissue is inadvertently removed along with the endometrioma wall [14]. This problem arises because endometriomas are coherent to the surface of the ovary and there are technical difficulties in separating the capsule from the healthy ovarian tissue [15,16]. Studies have shown that bilateral endometrioma surgery significantly increases the risk of premature ovarian insufficiency [17]. Because of the distinctive capsules of dermoid, musinous and serous cysts, in only 6% of cases healthy ovarian tissue is removed. However, in cases of endometrioma this ratio can raise up to 50% [14]. Although some studies showed that removed ovarian tissue is nonfunctional, others demonstrated healthy follicles in adjacent tissues. However, most of the studies observed functional ovarian tissues in examined materials removed around ovarian hilus [14]. During surgery a special attention should be paid to this region especially in infertile patients.

Does surgery restore fertility?

Whether the removal of endometriotic lesions (either by laparoscopy or laparotomy) would increase a woman's chance of spontaneous pregnancy via natural means is a quite complicated issue. This complexity arises from various forms of endometriosis (from superficial endometriosis, endometriomas to deep infiltrative endometriosis according to American Fertility Society) and different surgical methods that are applied [18]. The hypothesis which suggests that surgery improves the chance of spontaneous pregnancy is based on the reduction of pelvic inflammation [19]. The first findings in favor of surgery came from a randomized study [20]. The study, which included 341 women, has demonstrated that resection or ablation of visible endometriosis increased the fertility rates in a 36-week follow-up [20]. Subsequent supportive findings came from a meta-analysis [21], which takes these studies into account [20,22], and surgical approach (± adhesiolysis) was compared with diagnostic laparoscopy. This meta-analysis demonstrated that laparoscopic surgery increased fertility in minimal and mild endometriosis compared with diagnostic laparoscopy. The study, which has demonstrated no benefit, has been evaluated as 'questionable reliability' by Royal College of Obstetricians and Gynaecologists guideline due to small number of patients [23]. It is probable that there is an inverse relationship between the spontaneous pregnancy rates after surgical removal of endometriosis and the stage of endometriosis [24,25]. Findings show that the presence of endometriomas has a negative effect on ovarian physiology. Actually it has been calculated that ovulation rates of effected ovaries are halved compared with healthy ovaries [26].

Impact of different surgical methods on ovarian reserve & fertility

With advanced technology and changed patient demands in the recent years, now a concept has emerged in context of surgery playing a crucial part in enhancing *in vitro* fertilization outcome and fertility preservation. In the last 5-year period, many studies have evaluated the effect of endometrioma surgery on ovarian reserve by using a specific marker; serum anti-Müllerian hormone (AMH) level, and unfavorable effects of surgery on ovarian reserve were demonstrated. There are two systematic analyses that investigated pre- and postoperative AMH levels in patients who underwent laparoscopic extirpation of unilateral/bilateral endometriomas [5,27]. Early measurements within the first postoperative month generally demonstrated a significant decrease in AMH levels. This decrease was sustained through third, sixth, and even in the twelfth months in some studies [28]. In some others, AMH levels were observed to increase in the third month, although values were still lower than preoperative levels [29]. In two studies [30,31] conducted by the same group of researchers, there was no significant decrease in AMH levels after the operation. In bilateral cases, a more prominent decrease was also noted [5].

These perplexing results may be caused by different techniques used, and varying size and number of

endometrioma cysts reported in the studies. There have been increased amount of findings which demonstrated that surgical treatment of endometriomas did not improve response to ovarian stimulation with gonadotropins [32,33]. In support of these, various studies reported reduction in ovarian reserve following surgical treatment of endometriomas [32]. The ovarian injury is asserted to be caused by loss of healthy ovarian follciles during laparoscopic stripping, inflammation caused by surgical trauma or a probable vascular damage triggered by electrocoagulation [34]. Nevertheless, surgery may be offered in huge endometriomas probably due to enhanced response to controlled ovulation induction during IVF.

In a study [35] long-term findings of laparoscopic fenestration and coagulation of ovarian endometriomas were assessed and results were compared with that of ovarian cystectomy performed by either laparotomy or laparoscopy in 156 women with ovarian endometriomas of at least 3 cm in diameter. Cumulative clinical pregnancy and recurrence rates were similar after 36 months of follow-up between the groups. However, time to first pregnancy was significantly shorter in laparoscopic fenestration and coagulation group compared with patients undergoing cyctectomy by laparotomy.

In contrast, Alborzi *et al.* [36] found that laparoscopic cystectomy was a better choice than fenestration and coagulation in terms of recurrence and pregnancy rates in endometrioma surgery. At 1-year follow-up the cumulative pregnancy rates were 59.4% in the cystectomy group and 23.3% in the fenestration and coagulation group. In another interesting study Alborzi *et al.* [37] assessed follicular responses to controlled ovarian hyperstimulation between normal ovaries and ovaries previously treated by laparoscopic ovarian fenestration and coagulation, laparoscopic ovarian cystectomy and patients with bilateral endometrioma, cystectomy was done in one ovary and fenestration and coagulation in the contralateral side. There was no difference in response to controlled ovarian hyperstimulation between normal ovaries and those ovaries operated.

A Cochrane review on endometrioma surgery suggested that excisional surgery for endometrioma provided for a more favorable outcome than drainage and ablation with regard to the recurrence of the endometrioma, recurrence of pain symptoms, and in women who were previously subfertile, subsequent spontaneous pregnancy [38]. However, in women who may subsequently undergo fertility treatment insufficient evidence exists to determine the favored surgical approach. As similar, another meta-analysis has also suggested that laparoscopic stripping is superior to ablation and drainage when recurrence risks of symptoms and endometriomas as well as pregnancy rate were assessed [39]. However, the pregnancy rate was significantly higher for cystectomy compared with fenestration/coagulation, but not laser vaporization [39].

A systematic review of eligible studies assessed by Somigliana *et al.* [27] has supported a surgery-related damage to ovarian reserve. The magnitude of the decline was more evident in women operated on for bilateral endometriomas. In addition, the results of another systematic review and meta-analysis suggest a negative impact of excision of endometriomas on ovarian reserve as evidenced by a significant postoperative fall in circulating AMH levels [5].

The early postoperative reduction in AMH levels following endometrioma excision was observed to improve after 1 year of follow-up [40]. Notably, an inverse relation between the improvement in serum AMH levels and the number of follicles removed along with excised specimen was also emphasized. Almost all of the studies demonstrating an improvement indicate that AMH levels were unable to reach preoperative levels. Postponing surgery in possible future candidates of fertility surgery in the absence of current subfertility can be a rational approach.

Suturing for hemostasis instead of bipolar electrocoagulation may be suggested to prevent electroinjury. In a recent study, 100 patients with bilateral endometrioma were randomized to undergo hemostasis by either using laparoscopic suturing or bipolar coagulation after stripping of bilateral endometriomas [41]. Changes in ovarian reserve were investigated by measuring the levels of AMH and basal follicle-stimulating hormone before surgery and at 3, 6 and 12 months from surgery. In both study groups, postsurgical AMH levels were significantly lower and basal follicle-stimulating hormone levels were significantly higher than before surgery. There was no significant difference in the mean percentage decrease of AMH levels in the laparoscopic suturing or bipolar coagulation groups at 3-, 6- and 12-month follow-up. Pregnancy rate, time to conception, and rate of endometrioma recurrence was similar in the two study groups.

In a recent study we compared the effect of hemostatic matrix and electrosurgical bipolar coagulation on ovarian reserve in 30 patients with single ovarian endometrioma larger than 4 cm [12]. Ovarian reserve after laparoscopic excision of endometrioma was assessed by serum AMH. In each group, AMH levels were significantly higher in the third postoperative month as compared with first postoperative month. AMH levels were significantly lower in the electrosurgical bipolar coagulation group as compared with the hemostatic matrix group at first postoperative month. However,

the AMH levels were increased at third postoperative month which was similar between the groups [12]. This study suggested a beneficial effect of a hemostatic agent to provide ovarian hemostasis after endometrioma stripping in reducing compromise in ovarian reserve possibly caused by bipolar electrosurgical cautery [12].

Another study compared the results of laparoscopic cystectomy and laser vaporizationin a 5-year follow-up, especially in terms of recurrence rates [42]. In the early follow-up, the risk of endometrioma re-recurrence was higher after laser vaporization, however at the end of 60-month follow-up no statistically significant difference was observed between these two techniques regarding the recurrence risk of endometriomas [42].

Ovarian surgery in endometriosis patients should be performed by experienced surgeons with an aim to preserving ovarian reserve and improving fertility. Despite the available evidence indicating that the surgery for endometriomas does not improve ART outcome and may damage ovarian reserve, it seems that the majority of gynecologists offer ovarian cystectomy to their patients [43]. In a national cross-sectional survey, a total of 388 gynecologists fully registered with the Royal College of Obstetricians and Gynaecologists completed the questionnaire. The majority of responders were consultants (65%), 25% practiced ART and 65% performed laparoscopic surgery [43]. Overall, 95% of responders would offer surgery for endometriomas in women undergoing ART. The remaining 5% of responders would not offer surgery before ART. Excision was the most common surgical modality (68%), followed by ablation (25%) [43].

Assisted reproductive technologies & cryopreservation in women with advanced endometriosis

Preservation of fertility should be considered in all patients at serious risk of ovarian compromise before any surgical treatment of ovarian endometriomas. Fertility preserving techniques have been widely and increasingly utilized in patients with cancer, autoimmune or hematological diseases that will receive gonadotoxic therapies for years. Despite not frequent, various fertility preservation technologies have also practiced in patients facing the risk of compromised ovarian reserve due to ovarian surgery [44]. There are primarily three procedures: embryo, oocyte and ovarian tissue cryopreservation.

Embryo cryopreservation is the most widely performed technology. For years success rate of this approach has been higher than any other method that has been utilized. The success rates of IVF cycles using frozen thawed embryos now approach to or are even superior to fresh IVF cycles. When embryo cryopreservation is not feasible, especially in single women who do not wish to use donor sperm, oocyte cryopreservation can be preferred. Similar to embryo freezing, an ovarian stimulation cycle is also required that lasts about 2–4 weeks. Oocyte cryopreservation is another promising method of fertility preservation. With great advances in cryopreservation technology, especially with wider utilization of vitrification technology ASRM classified oocyte cryopreservation not an experimental approach anymore rather than an 'established technology' [45]. Ovarian tissue cryopreservation can be practiced at any time of the menstrual cycle without the need for ovarian stimulation. Notably, pieces of ovarian cortex harboring healthy ovarian follicles within the excised specimen can also be cryopreserved for possible future use. Moreover, this is the only technology that can be offered to prepubertal children facing the risk of ovarian failure due to gonadotoxic therapies or ovarian surgery. In the last 50 years, this field has rapidly progressed. A cryopreserved ovarian tissue was transplanted and ovarian functions were temporarily restored for the first time in the year 2000 in humans [46]. Approximately 18 successful pregnancies have been reported to date following ovarian cryopreservation.

As previously emphasized cryopreservation procedures are rarely applied for patients that will not recieve gonadotoxic therapies. Oocyte cryopreservation as a fertility preservation technique in patients with endometriosis was first reported in 2009 [47]. In this report, a single woman with severe pelvic pain that underwent multiple operations and unilateral oophorectomy was presented. Owing to the risk of further reduction in ovarian reserve caused by surgery, ovulation induction and oocyte cryopreservation were planned. Patient's basal antral follicle count was 3 and she had not responded sufficiently for the first two cycles. Antagonist protocol was applied for the third cycle and dosage of gonadotropins were increased. At the end of three cycles 21 MII oocytes were frozen. This report indicates that patients with endometriosis could also be candidates for cryopreservation [47].

It was previously shown that ovarian cortex surrounding ovarian cysts could be considered a source of ovarian tissue for future research. In a study by Schubert *et al.* [48], the cryopreservation procedure resulted in high follicular survival assessed by both histological and viability analyses. Orthotopic transplantation was applied to a patient with endometriosis 6 months after ovarian tissue cryopreservation [44]. Ovarian endocrine function and ovulation were observed in this patient for 9 months after transplantation surgery.

Conclusion

It has been among the most highly debated issues in reproductive medicine whether endometriomas should be operated in patients suffering from infertility. Despite definitive impact of endometrioma surgery in terms of improving fertility is still controversial, numerous reports indicate a reduction in ovarian reserve after surgery. Moreover, surgery increases the odds of premature ovarian failure especially in patients with bilateral endometrioma or in patients with multiple endometriotic cycts. Even though some studies suggest electrocoagulation after fenestration, cyctectomy seems more effective in terms of preserving fertility and preventing recurrences. Further large-scale studies are required to assess the definitive effect of alternative novel hemostatic techniques on ovarian reserve compared with electrocoagulation following cystectomy. It is also well established that recurrent ovarian surgeries cause significant damage to already diminished ovarian reserve; thereby a priority should be given to assisted reproductive technologies.

When surgery is inevitable in recurrent cases, available fertility preservation techniques should be exploited including embryo, oocyte or ovarian tissue cryopreservation. It is also crucial to underline that the current success rates of IVF using frozen thawed embryos/oocytes are almost identical to that using fresh oocytes/embryos. Success rates with ovarian tissue cryopreservation is still low, however, it is the only available technique that can be offered to prepubertal children facing the risk of ovarian compromise.

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Executive summary

- Whether endometriomas should be operated in patients suffering from infertility has been among the most highly debated issues in reproductive medicine.
- Despite the fact that definitive impact of endometrioma surgery in terms of improving fertility is still controversial, numerous reports indicate a reduction in ovarian reserve after surgery.
- Even though some studies suggest electrocoagulation after fenestration, cyctectomy seems more effective in terms of preserving fertility and preventing recurrences.
- It is also well established that recurrent ovarian surgeries cause significant damage to already diminished ovarian reserve; thereby a priority should be given to assisted reproductive technologies.
- When surgery is inevitable in recurrent cases, available fertility preservation techniques should be exploited including embryo, oocyte or ovarian tissue cryopreservation.

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