Endometriosis is a known cause of infertility in reproductive-aged women. Most treatment plans target pain caused by the disease, and may overlook the possibility that the patient may want to conceive. This review assesses current studies on fertility preservation in endometriosis patients and outlines the seven best methods to preserve fertility. We propose the following seven ways to preserve fertility in patients with endometriosis: choosing the best surgical techniques; avoiding unnecessary surgery; measuring ovarian reserve before surgery; emergency IVF before laparoscopic surgery; using a gonadotropin-releasing hormone agonist; maintaining a healthy lifestyle; and cryopreservation. Each endometriotic patient should be assessed on an individual basis, using these seven methods as guidelines, in order to maximize fertility preservation.

**Keywords:** emergency IVF • endometriosis • fertility preservation • gonadotropin-releasing hormone agonist • healthy lifestyle • in vitro fertilization • laparoscopic surgery • ovarian endometrioma • ovarian reserve

### Learning objectives

Upon completion of this activity, participants should be able to:

- Analyze lifestyle factors which can increase the risk of endometriosis
- Evaluate the role of gonadotropin-releasing hormone (GnRH) analogues among women with endometriosis and infertility
- Distinguish how to assess ovarian reserve among women with endometriosis and infertility
- Evaluate surgical options for women with endometriosis and infertility
Endometriosis is a disease in which the endometrial glands and stroma implant outside the uterine cavity. The disorder largely affects reproductive-aged women due to its connection to hormonal abnormalities [1]. Endometriosis is considered a benign gynecologic disease but it can potentially cause chronic pelvic pain and infertility [1].

Approximately 20–30% of patients with endometriosis are infertile. Therefore, there is an imperative need to find ways to increase fertility rates in women with this disorder [2]. It is estimated that endometriosis affects over 70 million women around the world; more than 30% of those women may also be infertile [3]. Animal studies have demonstrated that endometriosis results in decreased fertility, which suggests that there may be a correlation between them [4]. A study by Guzick et al. showed that fecundability decreased from 2.73 to 1.73% per month for patients with mild disease, and decreased further to 1.57% for patients with severe disease, thus implying that pregnancy rates significantly decrease as disease severity increases [4].

In patients with endometriosis, pregnancy rates are lower than normal, possibly because abnormalities in the endometrium prevent embryos from implanting in the uterus [5]. In order for an embryo to implant it must interact with the endometrium, attach itself to the epithelium and invade the decidualizing stromal compartment [5]. Moreover, dysregulated gene expression may alter mitotic activity, create toxic environments for the embryo, cause immune dysfunction, or promote apoptotic and inflammatory responses [5,6]. Problems with endometrial receptivity also occur in women undergoing assisted reproductive techniques (ART). Pregnancy rates of women with endometriosis who undergo IVF and embryo transfer (IVF–ET) are half that of women who undergo IVF–ET for tubal factor infertility [7].

Some treatments for endometriosis, especially surgery of ovarian endometrioma and hysterectomy for pelvic pain, can cause infertility and even induce early menopause. However, we suggest seven different approaches that women with this disorder can use to take a proactive approach to increase their chances of achieving pregnancy. These are (FIGURE 1):

- Choosing the best endometrioma/endometriosis surgical techniques;
- Avoiding unnecessary ovarian surgery;
- Measuring ovarian reserve (OR) before surgery;
- Utilizing emergency IVF before surgery;
- Using gonadotropin-releasing hormone (GnRH) analogs;
- Using cryopreservation techniques;
- Maintaining a healthy lifestyle.

These approaches have been supported by recent experiments and are the best options for promoting fertility in patients with endometriosis.

Choosing the best surgical techniques
Laparoscopy is considered the gold-standard treatment for ovarian endometriomas [8]. Various techniques that may be used include cystic wall laser vaporization, drainage and bipolar coagulation of the cystic wall, and endometrioma stripping; however, researchers still do not know which one is the most effective at avoiding ovary damage.

Surgery can lead to a reduction in OR by three main mechanisms: excessive stripping of the ovarian cortex, the use of bipolar coagulation to stop bleeding and the presence of surgery-induced inflammation [8–19].

It has been postulated that laparoscopic cyst stripping (cystectomy) results in a significant loss of normal ovarian cortex, which can reduce OR since the follicles lie within the cortex. In addition, there is rising concern that cystectomy is more harmful to the adjacent normal ovarian tissue than laser ablation [20].

Another group of researchers conducted a study using infertile women with unilateral disease who had undergone laparoscopic
stripping and had failed to conceive spontaneously. They found that the rate of severe ovarian damage at the point where the folliculogenesis and the ability of the ovary to release proficient oocytes was jeopardized was 13%. This damage can be caused by the removal of large amounts of healthy ovarian tissue or surgery-induced inflammation, among other reasons [20].

There has been increasing evidence that ovarian responsiveness drops after surgical treatment for ovarian endometrioma. According to Benaglia et al., out of 93 patients, 12 were nonresponsive after laparoscopic endometrioma cystectomy [20]. This is important to consider in women with bilateral disease, because if they undergo surgery on both ovaries they are likely to subsequently develop non-responsiveness to ovarian hyperstimulation and experience ovarian failure [10]. The rate of ovarian failure following surgery for bilateral endometrioma was reported to be 2.4% [21].

The potential reduction in OR attributed to surgery is especially important to consider in women with bilateral disease, asymptomatic disease and those undergoing IVF. Endometriomas may reduce the amount of functional ovarian tissue available by the space-occupying effect or by a local reaction. This effect is further aggravated by surgery, which increases the risk of lowering OR, resulting in surgically induced ovarian failure. The surgeon must weigh up the risks and decide whether surgery is essential or if a nonsurgical, conservative approach may be more beneficial at that time [22].

Most studies indicate that surgery is the best option in the treatment of large (≥4 cm) symptomatic ovarian endometriomas in infertile women. However, one question remains: do small asymptomatic endometrioma in infertile women require surgical treatment [23,24]? According to Busacca et al., surgery for bilateral endometrioma increases the risk of premature ovarian failure [21].

The study published by Nakagawa et al. in 2007 concludes that women with endometriomas bigger than 4 cm may benefit from surgery, not only for a correct diagnosis, but also for establishing a good pelvic anatomy and easily performing egg retrieval during IVF treatment. No significant change was noted in the ovulation rates preoperatively and postoperatively. However, in women with

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**Figure 1. Seven ways to reduce infertility in patients with endometriosis.**

COH: Controlled ovarian hyperstimulation; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone. Reprinted with permission from the Cleveland Clinic Center for Medical Art & Photography © 2011–2012. All Rights Reserved.
endometriomas smaller than 4 cm, a significant decrease in the ovulation rate was noted postoperatively [24].

This study found that the ovulation rate in the preoperative period was lower than normal on the side of the endometrioma (34.4 vs 50%) [16]. There was no significant difference in the pregnancy rate per ovulation cycle in the operated ovary compared with that of the intact ovary. The authors concluded that laparoscopic cystectomy reduces ovulation rates but maintains a normal pregnancy rate per ovulation [24].

Whether or not ovarian cystectomy decreases OR and pregnancy rates is a matter that is still being debated. Esinler et al. reported that ovarian cystectomy reduces OR as determined by a decrease in the number of oocytes obtained from the operated ovary; however, it does not translate into impaired pregnancy outcomes [25].

In a prospective study, infertile women with unilateral disease underwent either cystectomy or fenestration coagulation. In this study, women with bilateral disease underwent cystectomy on one ovary and fenestration coagulation on the other [26]. The number of dominant follicles obtained postoperatively by either surgical technique was comparable to women who had unilateral endometriomas. OR in the operated ovary was also comparable to that of the healthy ovary. Furthermore, the number of follicles obtained from either ovary postoperatively in women with bilateral disease was comparable [27].

In 2010, Benaglia et al. compared and contrasted the effects of cystectomy to a three-stage procedure for endometriomas. This procedure consisted of laparoscopic cyst drainage, followed by medical treatment with GnRH agonists for 3 months, and then laser vaporization using a CO\textsubscript{2} laser to eliminate any remaining endometriotic tissue. The authors found that the antral follicle count in the patients who underwent the three-stage procedure was significantly higher than that in the patients who underwent cystectomy, indicating that the former procedure was more effective at preserving OR [20].

According to Shimizu et al., the CO\textsubscript{2} laser causes significantly less damage to the ovary than electrocoagulation, as it is more precise, accurate and less detrimental to adjacent healthy ovarian tissue than electrocoagulation [28]. A study conducted by Shimizu and Takashima et al. in 2010 assessed the long-term effect of potassium-titanyl-phosphate laser ablation on ovarian endometrioma in infertile women. OR was assessed based on the number of oocytes retrieved from the ovary that had been ablated versus the contralateral ovary. No statistically significant difference was noted. The overall pregnancy rate (spontaneous and IVF-induced) was 75.6%. The results of this study seem to indicate that CO\textsubscript{2} laser may be used post-laparoscopic surgery [28].

In a study by Donnez et al., women who had undergone CO\textsubscript{2} laser vaporization of the cyst wall of ovarian endometriomas and then had failed to become pregnant for a year underwent IVF. No significant difference in pregnancy rates was found when the fertility rates were compared between the women with endometriomas and the women with tubal-factor infertility undergoing IVF. There was also no difference in the ovulation rates and the number of oocytes produced between the operated and contralateral ovary [27].

Laser ablation seems to be a good option for surgeons who want to decrease the chances of damaging ovaries. Laparoscopic cystectomy should be considered for endometriomas bigger than 4 cm that cause pain. In principal, it should be avoided when there is decreased OR. In order to choose the best ovarian endometrioma surgery technique, the recurrence rate should also be discussed with the patient [27].

To conclude, each case must be individualized; in addition, careful surgery by experienced hands limits damage to OR [27,29]. Surgery on women with endometriosis is difficult, and if it is performed by inexperienced surgeons or in poor conditions it may be strongly deleterious to OR; however, if it is carried out by experienced surgeons using careful, appropriate techniques, it may decrease the chances of negatively impacting OR. The surgical techniques should be improved, specifically optimizing two main aspects: preventing injuries to the follicular reserve that follows surgical excision of ovarian endometriomas; and preventing postsurgical formation and reformation of adhesions.

Avoid unnecessary surgery

While surgery is a common treatment for both pain and infertility caused by endometriosis, many procedures have been shown to have side effects that can cause a decline in fecundity [30].

Endometriomas affect 17–44% of women with endometriosis and can decrease oocyte quality and the efficacy of ART. Often, surgery is desirable to improve fertility outcomes in cases of endometriomas. However, the risks associated with surgery suggest that unnecessary surgical procedures should be avoided (Table 1) [23].

Of the surgical procedures used to treat endometriosis, cystectomy is cited most often as a procedure that negatively affects fertility. Since surgical techniques are primarily used to reduce pain, preserving fertility is not an immediate concern during cystectomy [22]. Various studies have shown that laparoscopic cystectomy can lead to ovarian tissue loss, a reduced follicular response, a decrease in ovarian follicle reserve, a reduced number of antral follicles and oocytes in IVF cycles, and reduced ovarian volume [22,31].

Although ovarian surgery can remove deleterious endometriomas in women with endometriosis, the procedure itself can diminish the amount of remaining ovarian tissue [30]. Bilateral cystectomy of endometriomas, in particular, has been shown to reduce serum anti-Müllerian hormone (AMH) levels [32]. A 2010 review by de Ziegler et al. suggests that if ART is necessary, GnRH-agonist treatment is another option for improving fertility in lieu of surgery [30].

Iwase et al. conducted a study in 2010 using serum markers and ultrasonographic markers to measure the functional potential of the ovaries and the quantity and condition of the follicles, in order to test the quality of OR in endometriosis patients [32]. They found that postoperative serum AMH levels were profoundly lower than preoperative levels in patients who had endometrioma [32]. It was concluded that laparoscopic ovarian cystectomy can reduce OR by damaging the ovaries [32].

There is a consensus in the literature that, in the presence of severe pain or endometriomas larger than 4 cm, surgical intervention is necessary, particularly given the impact that dyspareunia has upon spontaneous conception. However, this surgery should be avoided in several cases to preserve ovarian function that could be jeopardized by procedures. Specifically, surgery should be avoided for painless endometriomas <4 cm in size [23].
Cystectomy in particular should be avoided whenever possible due to the high prevalence of risks and complications cited [9,23,25]. According to a study by Vercellini et al. in 2009, surgery has limited benefit for minimal-to-mild-stage endometriosis. However, they reported a possible benefit in moderate-to-severe cases. No benefit was found for postoperative pain and recurrence rate, so surgery should be discouraged in these cases. When surgery is planned before IVF, only large endometriomas (>4 cm in size) should be removed [33]. The limit of 4 cm was established as a result of a consensus from various studies concluding that endometriomas of greater diameters cause problems for oocyte retrieval due to the possibility of punctured cysts, ruptures, infections and contaminations [34].

**Measure OR before surgery**

OR is defined as “the functional potential of the ovary [that] reflects the quality of the follicles left in the ovary in any given time” [32]. OR actually only represents a small percentage of the total OR, which consists of the number of follicles, including both the nongrowing follicles and the maturing, growing follicles. Functional OR usually refers to maturing, growing follicles only [32]. Another important term is ‘ovarian age,’ which is defined as the remaining reproductive capacity of a woman. In clinical practice, there is no method for measuring the nongrowing follicles; it is only possible to measure the functional OR [35].

To measure OR, numerous tests are available to assess fertility potential [36]. These tests can be divided into hormonal markers, ultrasound parameters and dynamic tests [36,37].

The exogenous follicle-stimulating hormone (FSH) OR is a test used to measure OR and predict IVF response rates. FSH, estradiol and inhibin B levels are measured before the administration of 300 IU of recombinant FSH on day 3. After 24 h, levels of estradiol should increase [36].

### Table 1. Laparoscopic endometrioma cystectomy and ovarian reserve.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Surgery technique</th>
<th>Methods used to assess OR</th>
<th>Effect of surgery on OR measurement</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnez et al. (2001)</td>
<td>Laparoscopic cystectomy</td>
<td>Stimulation parameters, fertilization, implantation and pregnancy rates</td>
<td>No change</td>
<td>[27]</td>
</tr>
<tr>
<td>Suganuma et al. (2002)</td>
<td>Laparoscopic removal of endometrioma</td>
<td>Number of retrieved oocytes</td>
<td>Decrease</td>
<td>[12]</td>
</tr>
<tr>
<td>Marconi et al. (2002)</td>
<td>Laparoscopic cystectomy</td>
<td>Estradiol levels, number of follicles, oocytes retrieved and clinical pregnancy rate</td>
<td>No change</td>
<td>[13]</td>
</tr>
<tr>
<td>Marconi et al. (2002)</td>
<td>Laparoscopic cystectomy</td>
<td>Number of gonadotrophin ampoules used for IVF–ET cycle</td>
<td>Increase</td>
<td>[13]</td>
</tr>
<tr>
<td>Loo et al. (2005)</td>
<td>CO₂ laser vaporization</td>
<td>Number of oocytes available for retrieval</td>
<td>Decrease</td>
<td>[31]</td>
</tr>
<tr>
<td>Esinler et al. (2006)</td>
<td>Laparoscopic cystectomy</td>
<td>Number of oocytes retrieved</td>
<td>Decrease (compared with nonoperated side)</td>
<td>[25]</td>
</tr>
<tr>
<td>Horikawa et al. (2008)</td>
<td>Laparoscopic cystectomy</td>
<td>Ovulation rate</td>
<td>Decrease</td>
<td>[23]</td>
</tr>
<tr>
<td>Iwase et al. (2010)</td>
<td>Bilateral cystectomy</td>
<td>AMH levels</td>
<td>Decrease</td>
<td>[32]</td>
</tr>
<tr>
<td>Almog et al. (2010)</td>
<td>Laparoscopic cystectomy</td>
<td>AFC, number of dominant follicles and number of oocytes collected</td>
<td>Decrease</td>
<td>[15]</td>
</tr>
<tr>
<td>Tsolakidis et al. (2010)</td>
<td>Three-stage procedure</td>
<td>AMH levels</td>
<td>Less diminished in three-step procedure group</td>
<td>[16]</td>
</tr>
<tr>
<td>Chang et al. (2010)</td>
<td>Laparoscopic ovarian cystectomy</td>
<td>AMH levels</td>
<td>Decrease</td>
<td>[17]</td>
</tr>
<tr>
<td>Pados et al. (2010)</td>
<td>Three-stage procedure</td>
<td>AFC</td>
<td>Increase in patients who underwent three-stage procedure</td>
<td>[18]</td>
</tr>
<tr>
<td>Hirokawa et al. (2011)</td>
<td>Laparoscopic cystectomy</td>
<td>AMH levels</td>
<td>Decrease (in both groups, but more in bilateral group)</td>
<td>[19]</td>
</tr>
</tbody>
</table>

AFC: Antral follicle count; AMH: Anti-Müllerian hormone; IVF–ET: IVF and embryo transfer; OR: Ovarian reserve.
In current practice, levels of FSH, AMH and antral follicle counts are used to measure OR [35]. These tests are sufficient preliminary tests for women undergoing IVF [36]. The use of AMH to measure OR seems to be increasing, whereas the use of FSH is declining [32]. The granulosa cells of growing pre-antral and small antral follicles produce AMH. It is more specific than FSH, and its levels do not vary with the phases of the menstrual cycle. Moreover, it is not affected by the use of oral contraceptives or GnRH analogs [32].

In another study by Hwu et al., women without endometriosis had higher AMH levels than those with the disease. Within the group of women with endometriosis, the patients who had undergone surgery had lower AMH levels than those who had not. This study concluded that patients with bilateral endometriomas had lower levels of AMH than those with unilateral disease [11]. In this study, AMH levels were measured prior to surgery, and four of the 31 women had very low serum AMH levels (<0.5 ng/ml), which increased their risk of postsurgical ovarian failure. This study concluded that it is imperative to assess OR prior to surgery so that women with low ORs can be identified and counseled appropriately. Although the stratification does not change the patient’s risk, OR should be measured in order to discuss the risks and benefits of surgery with the patient. If these patients are not identified prior to surgery, the aggressive nature of cystectomy could lead to ovarian failure.

The assessment of AMH levels prior to surgery could help the surgeon’s team to plan the best approach. In our opinion, the measurement of OR using AMH should be considered a routine test for patients undergoing surgery for ovarian endometriomas, so that surgery can be avoided in some cases and other methods such as egg or embryo freezing could be offered [11].

Surgery has an even greater effect on women older than 35 years of age. This may be explained by the fact that OR for these women is already reduced. We suggest that measuring OR prior to surgery can improve the chances by allowing the surgeon to optimize and individualize treatment modalities. If OR is reduced, aggressive surgery should be avoided.

**Emergency IVF before surgery**

The fourth method that should be considered when trying to reduce infertility in women with endometriosis is based on a recent review by de Ziegler et al. This article suggested that fecundity could be maximized in patients with endometriosis by choosing the optimal treatment mechanism based on the specific characteristics of the particular patient [30]. Among these potential treatments, the authors suggested a novel idea – that emergency IVF should be considered a routine test for patients undergoing surgery for ovarian endometriomas, so that surgery can be avoided in some cases and other methods such as egg or embryo freezing could be offered [11].

According to Carvalho et al., the ectopic endometrium of patients with endometriosis has been linked to the physiopathology of this disease [6]. This aberrant eutopic endometrium decreases the implantation rate leading to infertility in patients with endometriosis. Removing the pelvic disease itself through laparoscopy or laparotomy may not be the only immediate treatment for women with endometriosis and infertility, especially since the results of natural conception rates post-surgery are inconclusive [6,30].

Instead of immediate surgery, ovarian suppression before ART can repair endometrial differences and encourage receptivity. Surgery can reduce the amount of ovarian tissue and exacerbate the risk of infection at the time of oocyte retrieval for ART. However, surgery is ideal for those women who have an intact OR, unilateral disease, rapid growth, severe disease, debilitating pain or large endometriomas [30].

According to de Ziegler et al., surgery should not be the first line of treatment for patients who are older than 38 years of age, have an altered OR or have long-term infertility [30]. In these situations, emergency IVF should be performed that consists of IVF treatment before the patient undergoes surgery. If OR is intact, semen analysis should take place. In cases where the characteristics of the semen and the tubal status are incompatible with natural conception, immediate ART is also suggested. This is a novel approach and more studies should be done to better understand the real benefits of using IVF before treatment [30].

In other cases, surgery is recommended, but if spontaneous natural conception does not occur within 6–8 months postoperatively, emergency IVF should be performed. Following this protocol, the optimal treatment plan can be devised for each individual case of infertility in endometriosis patients.

**Use of GnRH analogs in patients with endometriosis**

The establishment, maintenance and growth of endometriosis depends on estrogen, and thus many treatment plans include hormonal therapy [38]. Unfortunately, most of these treatments, such as oral contraceptives, are targeted at managing pain and can prevent fertility [1,39].

GnRH is released by the hypothalamus, which leads to the secretion of FSH and luteinizing hormone from the pituitary, stimulating the ovary and thus causing follicular growth, ovulation and production of steroid hormones [40].

Artificial GnRH analogs work by increasing receptor affinity or decreasing the degradation of natural GnRH, which causes the sustained activation of GnRH receptors, thereby releasing gonadotropins stored in the pituitary [40]. Following their release, there is a downregulation of GnRH-receptor expression, which suppresses gonadotropin secretion, ultimately resulting in a drop in sex-steroid production in the ovaries. This generates a hypoestrogenic state that creates an unfavorable environment for the growth and maintenance of endometriosis [40].

The reduction of endometrial lesions by GnRH therapy alone, however, was shown to be more effective at relieving pain than promoting fecundity [40]. This is because GnRH agonists can prompt a ‘pseudomenopausal’ state in the hypothalamus–pituitary–ovarian pathway [38]. The GnRH agonists have a higher attraction to the GnRH receptor than the naturally occurring GnRH, so the natural female cycle is inhibited, the ovaries are
suppressed, and serum estrogen levels are reduced [38]. Several studies have shown that combining GnRH-agonist pretreatment with IVF improves fertility [39,41-43]. The advantages of GnRH therapy are maximized during the time of greatest disease suppression, so GnRH should be used immediately before IVF–ET is planned [39]. Surrey et al. showed that GnRH pretreatment 3 months before controlled ovarian hyperstimulation in infertile patients with endometriosis resulted in higher pregnancy rates and increased implantation rates after IVF–ET than controlled ovarian hyperstimulation alone, in patients under 40 years of age [39].

Dicker et al. showed that patients with stage III or IV endometriosis who were subjected to GnRH therapy 6 months before their IVF–ET cycle showed a 30% increase in pregnancy rates per cycle compared with patients who had undergone a standard controlled ovarian hyperstimulation [42].

GnRH-agonist treatment may be effective in reducing infertility because it has been shown to lead to an increase in natural killer-cell activity, possibly owing to the GnRH itself or the resulting elevated estradiol levels [39]. It also increased antibody levels, resulting in higher peritoneal fluid levels of IL-1 and decreased levels of TNF-α [39]. According to Surrey et al., the GnRH agonists also affect cell apoptosis and obliterate the embryotoxic effects of peritoneal fluid [39].

Studies have shown that GnRH-agonist treatment results in increased natural killer-cell activity and diminished embryotoxic effects of peritoneal fluid in women with endometriosis. This treatment can also reduce the size of ovarian endometriomas [44].

In general, GnRH agonists have been found to increase IVF success rates in endometriosis patients. According to Coccia et al., ovarian parenchyma damage during the surgery seems to be related to cyst diameter. Since GnRH reduces the size of the cyst, it may be useful in reducing ovarian damage when it is used prior to surgery [36,45].

Cryopreservation in patients with endometriosis
Surgical procedures such as endometrioma excision can result in a reduction of OR due to the loss of normal ovarian tissue and follicles. One out of every 42 women experiences instantaneous menopause after bilateral excision [46]. Women with endometriosis who desire pregnancy should consider egg donation or cryopreservation as methods of fertility preservation if they have low ORs [46-48].

Although embryo cryopreservation is the standard procedure, cryopreservation can be used in women without male partners or in prepubertal girls through methods such as ovarian tissue cryopreservation and egg freezing [46]. Ovarian tissue can be cryopreserved through two types of surgery: excision of the ovarian tissue and autografting [46]. Cryopreservation was first developed by Sherman et al. using mouse oocytes, and has evolved to involve slow freezing then rapid thawing, a method initiated by Whittingham that yields a pregnancy rate of 25% [49,50].

Another method, called vitrification, involves the solidification of an aqueous solution by ultra-rapid cooling. This process has been proven to be more successful than the slow-freezing/rapid-thawing method in terms of oocyte survival, implantation and clinical pregnancy rates [46]. Vitrification is a cryopreservation technique that uses high concentrations of cryoprotectant to solidify cells in a glass state without ice formation. It also uses carbohydrate-penetrating cryoprotectants to assist with the dehydration process [51]. A study conducted at the McGill Reproductive Center (Montreal, Canada) found that vitrified oocytes had a survival rate of 85%, a fertilization rate of 75% and a pregnancy rate >40% [51].

Another study conducted by Katayama et al. showed that among 46 vitrified oocytes, there was a 94% survival rate, a 91% fertilization rate by intracytoplasmic sperm injection (ICSI) and a 90% cleavage rate. Two out of six tests resulted in pregnancy [52]. Recently, two other manuscripts reinforce that vitrification would be a safe and highly successful cryopreservation technique [53,54]. Rienzi et al. reported that the survival rate of sibling-vitrified oocytes was 96.8% and the fertilization rate after ICSI was 76.6% [54]. Cobo et al. tested four different protocols with the vitrification technique and found similar spindle configurations (81, 73.9, 88.9 and 81.3%, respectively) versus 88.5% for controls [55].

In prepubescent girls, immature oocyte cryopreservation is the only method for preserving fertility. However, using prophase I germinal vesicles increases the risk of zona pellucida hardening, chromosomal aneuploidy, karyotype abnormalities, organ malfunctions and damage to the cytoskeleton [55,56]. In order to prevent the zona pellucida from hardening, ICSI is a suitable option [51].

Another method, known as ovarian tissue cryopreservation, involves reimplantation of cortical ovarian tissue into the pelvic cavity or a heterotopic site. After the completion of treatment and once patients are disease-free, the implanted tissue can then be used in an IVF–ET procedure [55]. This method is associated with a 25% follicle survival rate, but is most successful when patients are younger than 40 years of age.

There is evidence to suggest lower birthweights of babies conceived through cryopreservation; however, these babies have normal growth rates after birth [57]. Just as birth defects and chromosome abnormalities can occur with the use of ART, there is also a risk for these complications with cryopreservation and fresh IVF [57].

Some studies show comparable rates of preterm births and low birthweight between cryopreservation embryo transfer and IVF–ET; however, others have failed to find the same results. The authors concluded that more studies are needed on all cryopreservation techniques, and that there is no clear indication of using cryopreservation instead of embryo transfer [57]. While cryopreservation is still a largely experimental method, approximately 500 live births have been reported using cryopreserved oocytes, and recent developments suggest that it is an encouraging method for endometriosis patients facing infertility [58].

In conclusion, infertile endometriotic patients undergoing IVF who have partners should cryopreserve their remaining embryos. Patients who have compromised OR and do not have partners should consider oocyte cryopreservation using vitrification techniques. Adolescent patients with endometriosis who must undergo surgery for endometriomas, and patients with ovarian cancer, should consider cryopreserving ovarian tissue in an attempt to...
Table 2. Summary of the manuscripts included in this review.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Method/condition</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choose the best endometrial/endometriosis surgical techniques</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alborzi et al. (2007)</td>
<td>Cystectomy vs fenestration/coagulation</td>
<td>No difference</td>
<td>[26]</td>
</tr>
<tr>
<td>Donnez et al. (2001)</td>
<td>Endometriosis surgery by internal wall vaporization</td>
<td>Does not impair IVF outcome</td>
<td>[27]</td>
</tr>
<tr>
<td>Pados et al. (2010)</td>
<td>Laparoscopic cystectomy vs three-stage procedure</td>
<td>Functional ovarian tissues higher after three-stage procedure</td>
<td>[18]</td>
</tr>
<tr>
<td>Shimizu et al. (2010)</td>
<td>Laparoscopic ablation surgery</td>
<td>75.6% pregnancy rate</td>
<td>[28]</td>
</tr>
<tr>
<td><strong>Avoid unnecessary surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benaglia et al. (2010)</td>
<td>Endometrioma surgery</td>
<td>Ovarian damage</td>
<td>[20]</td>
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<tr>
<td>Horikawa et al. (2008)</td>
<td>Laparoscopic cystectomy</td>
<td>Reduces frequency of ovulation</td>
<td>[23]</td>
</tr>
<tr>
<td>Iwase et al. (2010)</td>
<td>Laparoscopic cystectomy</td>
<td>Postoperative decrease of serum AMH level</td>
<td>[32]</td>
</tr>
<tr>
<td>Var et al. (2011)</td>
<td>Coagulation/cystectomy</td>
<td>Decrease in AFC/ovarian volume</td>
<td>[22]</td>
</tr>
<tr>
<td>Loo et al. (2005)</td>
<td>Ovarian cystectomy for endometriomas</td>
<td>Fewer oocytes harvested during IVF</td>
<td>[31]</td>
</tr>
<tr>
<td><strong>Measure ovarian reserve before surgery (AMH, AFC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iwase et al. (2010)</td>
<td>Serum AMH</td>
<td>Useful marker of ovarian reserve after cystectomy</td>
<td>[32]</td>
</tr>
<tr>
<td><strong>Emergency IVF before surgery</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Using GnRH in endometriosis patients</strong></td>
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<td>Ruhland et al. (2011)</td>
<td>GnRH agonist</td>
<td>Pain reduction</td>
<td>[38]</td>
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<td><strong>Role of lifestyle in endometriosis</strong></td>
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<td>Tavmergen et al. (2007)</td>
<td>GnRH agonist before IVF</td>
<td>Higher pregnancy rates</td>
<td>[41]</td>
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<td>Cramer et al. (1986)</td>
<td>Smoking and exercise</td>
<td>Decreases risk of endometriosis</td>
<td>[65]</td>
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<td>Cramer et al. (2002)</td>
<td>Smoking and exercise</td>
<td>Decreases risk of endometriosis</td>
<td>[61]</td>
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<td>Caffeine and alcohol</td>
<td>Increases risk of endometriosis</td>
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<td>Missmer et al. (2004)</td>
<td>High body mass and alcohol</td>
<td>Increases risk of endometriosis</td>
<td>[63]</td>
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<tr>
<td>Vitois et al. (2010)</td>
<td>High body mass</td>
<td>Increases risk of endometriosis</td>
<td>[62]</td>
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<tr>
<td>Nagle et al. (2009)</td>
<td>Late childhood obesity</td>
<td>Increases risk of endometriosis</td>
<td>[64]</td>
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<tr>
<td>Missmer et al. (2010)</td>
<td>Specific dietary fat (trans-fat)</td>
<td>Increases risk of endometriosis</td>
<td>[69]</td>
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<td><strong>Egg donation and cryopreservation</strong></td>
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<tr>
<td>Elizur et al. (2009)</td>
<td>Fertility preservation</td>
<td>Good preoperative counseling for women with severe endometriosis</td>
<td>[46]</td>
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<td>Oktay et al. (2001)</td>
<td>Ovarian tissue and oocyte cryopreservation</td>
<td>Sustains reproductive function in a select group of women</td>
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<td>Katayama et al. (2003)</td>
<td>Oocyte vitrification</td>
<td>Preserves fertility</td>
<td>[52]</td>
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<tr>
<td>Garrido et al. (2002)</td>
<td>Egg donation from nonendometriosis patient</td>
<td>Overcomes hostile uterus environment</td>
<td>[47]</td>
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</table>

preserve their fertility. In our opinion, optimal egg donors should not have endometriosis, as they may have a decreased number of oocytes and poor embryo quality, which could lead to lower implantation rates. More studies, specifically randomized control trials, are needed for a better understanding of the mechanisms of fertility preservation using cryopreservation [59,60].

Role of lifestyle in infertile patients with endometriosis

As obesity, alcohol intake and smoking rates increase, it is important to study their effects on endometriosis and to stipulate lifestyle modifications, not only for overall health concerns, but also to improve fertility [61]. As the term ‘modifiable risk factors’ suggests, these habits can be altered and risks can be greatly lowered. Numerous studies have been conducted to establish the effect of lifestyle modifications on endometriosis and infertility. Endometriosis is an estrogen-dependent disease, so any lifestyles that reduce the production of estrogen may reduce the risk of endometriosis [61,62].

Bodyweight & exercise

Various studies have shown that endometriosis may actually be more common in tall, lean women than in heavier women [61,63].

A study by Nagle et al. confirmed that because obese girls reach menarche at a younger age, they are exposed to more retrograde flow as well as higher estrogen levels due to estrogen formation in adipose tissue by aromatase enzyme. Leptin and adiponectin, which are found in excess in obese children, may also play a part in the development of endometriosis [63].

A study by Missmer et al. showed an inverse relationship between BMI at 18 years and endometriosis. A decreased risk was also noted in overweight and obese females with concurrent infertility. The authors correlated these findings with the higher prevalence of oligomenorrhea among obese women. This may explain their increased risk of infertility and decreased risk of endometriosis [63].

Women with a BMI >30 generally have irregular cycles and may suffer from anovulatory cycles, which may reduce the risk of endometriosis; however, despite the discrepancies regarding weight and endometriosis, it is thought that exercise reduces the risk of endometriosis [61]. Women who started exercising at a younger age and exercised regularly, defined as more than 2 h per week, were at a lower risk [63]. This may be explained by the fact that regular exercise lowers estrogen levels [66,67].

The correlation between BMI and the risk of developing endometriosis is still controversial in the literature. Better-designed studies still need to be conducted to further understand this association.

Diet

Parazzini et al. reported a positive association between endometriosis and red meat consumption, and a negative association between endometriosis and fruit and vegetable consumption [68].

A study conducted by Missmer et al. in 2010 found an increased risk of endometriosis with the consumption of palmate acid, a major component of animal fat; however, there was no relation between total fat intake and endometriosis. There was an increased risk with high consumption of trans-fats; however, consumption of omega-3 fatty acids reduced this risk. Women who reported infertility and consumed large amounts of trans-fats were at a 72% greater risk of endometriosis than those who consumed smaller amounts of trans-fats [69].

Smokers who consumed trans-fats were at a much higher risk of endometriosis than nonsmokers. Overall, 78% of the trans-fat contribution came from industrially prepared foods, and was likely produced from the partial hydrogenation of vegetable oils. This study shows that diet, which is a modifiable risk factor, may be important in the etiopathogenesis of endometriosis [69].

Smoking, alcohol & caffeine

The correlation between smoking and endometriosis has been the subject of conflicting results among many studies. One study claimed that among women without infertility problems, there was a positive relationship between smoking and endometriosis, but among women who were infertile, there was an inverse relationship between current smoking and endometriosis. The effects of smoking may be explained by the fact that while smokers are generally estrogen-deficient, they are also exposed to higher levels of environmental pollutants, such as dioxins, that have hormone-like qualities [69].
Other studies have found an inverse relationship between smoking and endometriosis. These studies show that the incidence of endometriosis was lower in women who started smoking at a younger age (<17 years) and smoked more than one pack a day than those who began later in life and smoked less frequently. Smoking has been found to lower estrogen levels [61,65]. Some studies stipulate that caffeine and alcohol both increase estrogen levels, and thus the risk of endometriosis [61]. Another study found that women who had higher alcohol intakes had lower rates of endometriosis despite the increased estrogen levels seen with moderate alcohol intake. However, the validity of this study is questionable, as the investigators only examined the effects of consuming more than one drink per day [63]. Nonetheless, the hazardous health effects of smoking and alcohol consumption far outweigh their potential benefit in regards to endometriosis and infertility.

Sexual dysfunction
Lastly, couples experiencing dyspareunia engage in less frequent sexual intercourse, and report sexual dysfunction in both the female and male partners, potentially decreasing fertilization [70]. The role of lifestyle in infertile patients with endometriosis is still a controversial topic. Indeed, our conclusions should be considered to contribute to the development of new strategies to overcome endometriosis and associated infertility [63].

Expert commentary
After an extensive search for recent studies and articles (Table 2), these seven precautions were determined to provide the best options for maximizing fecundity in endometriosis patients. It is important to understand that treatment should be individualized. However, these guidelines should be considered as preliminary measures to prevent and treat infertility.

Five-year view
There is increasing evidence from the literature that there is an association between endometriosis and infertility, but a definite cause and exact relationship has not yet been established. Many published studies have shown that endometriosis decreases IVF outcome. New strategies of fertility preservation in patients with endometriosis, and a better understanding of how endometriosis affects fertility, will probably increase ART outcomes.

In 5 years, better ART methods may be available to make IVF outcomes in patients with endometriosis comparable to patients without the disease. Ideally, the advancement of vitrification and cryopreservation may produce better results for patients with endometriosis, with oophorectomy being performed only in rare cases of endometriosis associated with ovarian cancer.

Gynecologists must be able to perform surgery with the best technology available in order to decrease the impact of surgery on OR and improve pregnancy rates in patients with endometriosis. Promising new technologies to create less invasive alternatives to treat endometriosis will benefit many with the disease. In the future, robotic, single-site surgery (laparoendoscopic single-site surgery) and single-port laparoscopy may be used to perform ovarian surgery without massive damage, provided it is performed by a highly skilled surgeon.

References
Papers of special note have been highlighted as:
• of interest
** of considerable interest
10 Somigliana E, Arnoldi M, Benaglia L, Iemmello R, Nicolosi AE, Ragni G. IVF–ICSI outcome in women operated on
Seven ways to preserve female fertility in patients with endometriosis

Review

www.expert-reviews.com


First author to suggest the idea of emergency IVF in patients who have a decrease in ovarian reserve.


42 Dicker D, Goldman JA, Levy T, Feldberg D, Ashkenazi J. The impact of long-term gonadotropin-releasing hormone analogue treatment on preclinical abortions in patients with severe endometriosis.


- Describes a successful vitrification technique, even after 5 years of cryopreservation.


- Suggests the novel and strong correlation between food consumption and risk of developing endometriosis.

Seven ways to preserve female fertility in patients with endometriosis

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 70% passing score) and earn continuing medical education (CME) credit, please go to http://www.medscape.org/journals/expertob. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the New Users: Free Registration link on the left hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association’s Physician’s Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/category/2922.html. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate and present it to your national medical association for review.

Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

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<tr>
<td>1. The activity supported the learning objectives.</td>
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<td>2. The material was organized clearly for learning to occur.</td>
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<td>3. The content learned from this activity will impact my practice.</td>
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<td>4. The activity was presented objectively and free of commercial bias.</td>
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1. You are seeing a 32-year-old woman who was diagnosed with endometriosis 6 months ago. She has been trying to conceive her first child with her husband for the past 15 months. The patient wants to know more about why she has endometriosis. What can you tell her is the most established lifestyle or anthropometric risk factor for endometriosis?

- A Tall stature with low bodyweight
- B Inadequate consumption of palmate acid
- C Cigarette smoking
- D Abstinence from alcohol

2. You decide to treat this patient with a gonadotropin-releasing hormone (GnRH) analogue. What should you consider regarding this therapy?

- A Treatment leads to an upregulation of GnRH receptors
- B GnRH analogues are more effective in improving fecundity than reducing pain
- C GnRH analogues should be avoided around the time of in vitro fertilization and embryo transfer (IVF-ET)
- D Overall, GnRH analogues improve the success of IVF in cases of endometriosis

3. All of the following studies should be employed to measure ovarian reserve (OR) in this patient EXCEPT:

- A Serum estradiol
- B Serum FSH
- C Serum AMH
- D AFCs
4. Eventually, it is decided to perform surgery on the patient from Question 1. What should you consider regarding surgery for endometriosis and fertility?

- A. Cystic wall laser vaporization is the best technique to treat ovarian endometriomas
- B. Drainage and bipolar coagulation of the cystic wall is the best technique to treat ovarian endometriomas
- C. Cystectomy is most often cited as a surgical procedure for endometriosis that negatively affects fertility
- D. Painless endometriomas 2 to 4 cm in size should be removed to improve fertility