REVIEW ARTICLE

How to Protect Fertility Potential in Endometriosis

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Abstract

Endometriosis is a chronic condition affecting fertile women with many adverse effects. Subfertility is one of the main issues. The ovarian reserve (OR) gradually decreases due to physical and immunological factors associated with endometriosis. Hence, early and prompt treatment of endometriosis and subfertility caused by endometriosis can improve a woman's quality of life. The article aims to shed light on the currently available options for fertility-preserving management of endometriosis. Endometriosis-related subfertility should be managed judiciously and individually according to age, parity, the extent of the disease, and the patient's social aspect. Subfertility management is approached by medical management but sometimes demands a surgical approach. But, surgery is very detrimental to OR. That is why, while managing endometriosis, one should aim to protect fertility potential. To approach fertility protection, suppressive therapy, which halts the disease process and prevents follicular loss due to "OMA," is an option for adolescents and women who want to postpone pregnancy for a certain period. If one needs surgical intervention for treatment, a modified surgical approach to minimize follicular loss would be preferable to protect the OR. Also, while treating subfertility, the approach should be to reduce the time to live birth to avoid the consequences of the recurrence of the disease. And finally, in adolescent endometriosis and women who need repeated surgery, fertility preservation by tissue freezing might help them for future fertility in the present day.

Keywords: Aromatase inhibitors, Endometriosis, Fertility preservation, GnRH agonist, GnRH antagonist, Modified surgery, Ovarian reserve.

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Introduction

Endometrial tissue can be found outside the uterus's natural endometrial chamber in endometriosis, a chronic inflammatory disease. It is one of the most prevalent causes of chronic pelvic pain (CPP) and affects 5–10% of women of reproductive age.[1] The most typical symptoms are dysmenorrhea, dyspareunia, dyschezia, and abdominal pain, and 30–50% of women with endometriosis are infertile.[2,3] Endometrioma's etiopathogenesis is yet unknown. However, numerous theories are beginning to emerge. The basis of changes in endometrioma is the invagination of the ovarian cortex and the creation of a pseudocyst following bleeding from a superficial endometriotic implant and the buildup of blood within the cyst.[4,5] According to Nezhat et al.,[6] functioning cysts convert into endometriomas. The origin of endometrioma is associated with metaplasia of invaginated coelomic epithelium, according to Donnez et al.[7] Estrogen progesterone signaling is disrupted in endometriotic tissue,[8] which can be induced by many endocrine-disrupting chemicals (EDC). Phthalates are known EDCs with estrogen-like activity potential, which is linked to causing endometriosis in humans.[9,10] It is primarily used as a consumer product in industry as a solvent, additive, and plasticizer.[11]

The cause of infertility in endometriosis-affected women is unknown, and several potential contributing variables exist. Adhesion, cytokine, altered immunity, and follicular damage are responsible for infertility. As endometriosis is an adhesive disease, there is anatomical distortion and compression of tubes, leading to distortions of the tubo-ovarian relationship, cyst, and endometrioma formation. As the disease is recurrent and progressive, treatment might demand repeated surgery. Either single or repeat surgery is always detrimental to ovarian reserve (OR). The protection of endometriosis patients' reproductive potential should therefore be the priority. This evaluation concentrated on the disease's negative aspects and emphasized endometriosis care that safeguards and maintains reproductive function.

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What Happens in Endometriosis?

Endometriosis causes infertility in many different ways. The most devastating abnormality is the distortion of pelvic anatomy, which interferes with ovum pickup and transportation by fallopian tubes.[12] Secondly, altered immunity, inflammatory process, and cytokine-rich peritoneal fluid interfere with tubal motility, sperm motility, fertilization, embryonic development, and viability.[13–20] Also, follicular damage in endometriosis causes a gradual decline of OR and leads to early menopause.[21] Implantation failure in endometriosis patients is due to abnormalities of the eutopic

endometrium.[12] Reduced endometrial receptivity (ER) and disruption of the luteal phase are caused by progesterone resistance resulting from progesterone receptor dysregulation.[14,16,22,23]

Reduction of Ovarian Reserve

Due to the illness and cortical tissue fibrosis, ovarian follicles diminished in endometriosis patients. A consequence of focal endometriotic inflammation could be fibrosis.[24] In endometriosis-affected ovaries, local inflammation may directly impact follicular apoptosis and atresia. Early folliculogenesis may be stimulated in ovaries with endometriomas compared with contralateral ovaries without cysts, and follicular atresia rises. In ovaries with endometriomas, recruitment may be upregulated, and early follicles may die, leading to focused exhaustion of primordial follicles that make up the low OR.[25] Ovarian vascularization may be decreased in endometriosis. Elevated oxidative stress in endometrioma from all mechanisms may promote follicle activation and atresia, altering the formation of antral follicles, lowering follicular count, and decreasing focal AMH.[26] This enables further follicular recruitment and ensuing atresia. Follicle depletion and a diminished OR result from this vicious cycle and "burnout" processes in endometriosis.[27,28] Follicles in the afflicted ovary exhibit a decreased OR and share some physiological traits with aging ovaries.[29] Larger pool, healthier follicles are drawn from the ovary in women in their 20s and early 30s, whereas those in their late 30s may exhibit a shrinkage in size. Due to fibrosis and inflammation, follicular density is dramatically decreased in endometriosis-affected women.[24,30]

Deterioration of Oocyte Quality

Oocyte quality is adversely impacted by endometriosis in numerous ways. According to several studies, endometriosis and endometrioma may impair ovarian steroidogenesis by reducing P450 aromatase expression.[31] Granulosa cells (GC) might suffer negative consequences due to an altered cell cycle,[32] increased apoptosis,[33] and dysregulation of the molecular pathways governing GC development and proliferation[34,35] Reactive oxygen species (ROS) from oxidative stress have been demonstrated to enhance meiotic abnormalities and chromosomal instability, lowering the quality of oocytes.[36] Oxidative stress is a key pathophysiological component in endometriosis. Also, as shown by greater amounts of iron in the follicular fluid (FF) of follicles adjacent to the endometriotic cyst compared with contralateral healthy ovaries, endometrioma iron from chocolate substance promotes oxidative damage to the surrounding follicles.[37] Endometriosis-related inflammatory cytokines may alter folliculogenesis and be a factor in poor oocyte quality.[38,39] Goud and colleagues discovered that endometriotic women's oocytes had increased zona pellucida stiffening and cortical granule loss, which interfered with fertilization and the capacity of an embryo to undergo hatching. There was a greater aberrant spindle in oocytes reported to women receiving ART due to endometriosis compared with male factor infertility (66.7 vs 16%).[40]

Low and Abnormal Mitochondrial Content

The cornerstone of the cell's power is its mitochondria. Normal chromosomal segregation, a cell division requirement, will not occur if the mitochondrial count decreases. Compared with other cell types, mature oocytes' cytoplasm has a very high concentration of mitochondria.[41–43] Oocytes from endometriosis-afflicted women showed fewer mitochondria and aberrant mitochondria with tiny or enlarged, blurry vacuoles. Low mtDNA concentration indicates lower oocyte quality in women with mild or moderate endometriosis.[44]

Effect of Surgery on Ovarian Reserve

It is generally known that endometriosis patients have altered serum AMH levels. Patients with moderate-to-severe endometriosis, particularly those with bilateral endometriomas, experienced striking drops in serum AMH. AMH is further decreased by surgery on these endometriomas. One of the main findings of endometriosis is a decreased follicular pool.

Over stripping of the ovarian cortex, thermal coagulation to halt the bleeding after stripping, and inflammation brought on by surgery were the mechanisms of decreased follicular pool.[45,46] Bilateral endometrioma surgery was associated with a 2.4% reported probability of ovarian failure.[47] In 69% of cases, primary and secondary follicles can be seen in the ovarian tissue that was removed together with the endometrioma wall at the ovarian hilus, according to Muzii et al.[48] Hence, a significant amount of the follicular pool is lost after surgery, especially when the hilum is implicated. As a result, the endometrioma wall and ovarian tissue are prevalently unintentionally removed during endometrioma excision. Moreover, abundant circulation at the hilar region causes bleeding during the separation of the cyst and leads to thermal coagulation for controlling bleeding, further destroying follicles.

Effect of Repeat Surgery on Fertility Potential

Due to the absence of an anatomically discernible cleavage plane in 44–81% of patients with endometrioma, significant healthy ovarian tissue was unintentionally removed during cystectomy.[49–55]

In comparison to a group of patients being operated on for the first time, Muzii et al. reported on a series of patients who had surgery for the recurrence of a unilateral ovarian endometrioma. The postoperative OR by antral follicle count (AFC) and ovarian volume and histological findings of the cyst wall in the two groups were compared. Compared with the group that underwent initial surgery (1.1 mm), the excised cyst wall (1.7 mm) in the recurrent group was much thicker. The AFC and ovarian volumes on the operated side were considerably lower than those of the non-operated ovary in the group with recurrent endometrioma.[56]

Possible explanations include: (a) Due to higher concentrations of free iron, ROS, proteolytic enzymes, and inflammatory molecules, recurrent endometrioma may be more aggressive in damaging healthy ovarian tissue and result in greater damage to the adjacent ovarian cortical tissue.[35] (b) The presence of the first endometrioma and the first surgical operation may have already caused damage to the ovary with the recurrent endometrioma; (c) The fibrosis brought on by the first surgery makes the second surgical procedure more difficult and harmful. Therefore, a greater loss of ovarian tissue is linked to surgery for recurring endometriomas. Moreover, OR is harmed more by a second surgery than a first one.

How to Protect the Ovaries and Ovarian Reserve of Women with Endometriosis?

Endometriosis is an incurable and recurrent disease, but no disease prevention exists. So the only way to protect the ovaries is by halting the progress of the disease through early diagnosis and treatment. Diagnosis of the disease at the earliest stage is of the utmost importance. Endometriosis usually occurs within the reproductive age group but, in rare cases, may occur beyond that age group. It occurs in younger girls as young as eight, before puberty. Management is relatively less cumbersome by medical

and surgical means if women are older and have completed their families. But deciding on treatment options for young adolescent girls is difficult. Diagnosing the disease takes a long time and usually takes 7–11 years.[57] As a result, the disease progresses gradually, and girls often present at the advanced stage. The main aim is to relieve the symptoms, halt the disease's progression, and protect the girl's future fertility. Endometriosis in adolescents necessitates ongoing medical treatment until the point in their life when they are ready to have children. Psychosocial support is very important for these young women with endometriosis.

Approaches of Treatment for Fertility Protection

- Suppressive therapy stops the disease process and prevents follicular loss due to endometrioma.
- Modified surgical approach to minimize follicular loss during surgery.
- Approaches for reduced time to live birth.
- Fertility preservation.

Suppressive therapy: Endometriosis requires a lifelong care plan, according to the ASRM Practice Committee,[58] to maximize the use of pharmaceutical medications and prevent recurring surgical procedures. All of the endometriosis treatments that are now available are suppressive rather than curative.

Hormonal Therapy

Hormonal treatment suppresses the disease and reduces the need for surgery by halting the disease at an earlier stage. By preventing ovarian activity (including the release of endocrine sex hormones) or by directly interfering with steroid receptors and enzymes in lesions and endometrium, the prescribed drugs change the hormonal environment. Avoiding surgery minimizes ovarian damage and preserves OR. Postoperative suppressive hormone therapy improves disease progression in women with persistent or recurring diseases.

All hormones relieve the symptoms related to the endometriotic implant and reduce the growth of the endometriotic implant. Some hormones inhibit follicular growth and ovulation, decrease estrogen production, make the environment hypo-estrogenic, and suppress ectopic endometrial growth. Others directly inhibit the growth of the endometriotic focus. Due to atrophy of the endometrial focus, women become amenorrheic, preventing cyst formation. Hormonal treatment is effective and well-tolerated in about 70% of women.

The following hormones are used for endometriosis:

- Combined oral contraceptive pill (COCP)
- Progesterone
- GnRH agonists
- GnRH antagonist
- Aromatase inhibitors
- Cabergoline

Combined Oral Contraceptive Pill (COCP)

The COCP is used continuously or cyclically. Continuous therapy is more effective than cyclical in women with cyclical pain. It is cheap, easily available, and well-tolerated with mild side effects. It prevents ovulation and makes women amenorrheic, reducing pain and disease progression.

It is better to avoid it in girls younger than 16, as it may interfere with a growth spurt. Relative contraindications are women over 35 with hypertension, cardiovascular disease, and venous thrombosis. A meta-analysis involving 965 women reported postoperative long-term OCP use significantly reduces recurring endometrioma.[59]

Progesterone

Progesterone can be used in many forms and acts via multiple routes like oral, intramuscular injection, subcutaneous insertion (implant), and an intrauterine device (LNG). Commonly used drugs are norethisterone acetate, Medroxyprogesterone acetate, and Levonorgestrel-releasing intrauterine systems (LNG), which can give support for five years. Dienogest 2 mg daily can be given for sixty months (five years).[60] This drug can be used for a long time for young adolescents and unmarried girls.[61,62] It causes endometrial glandular atrophy, modifies estrogen receptor activity, and inhibits the growth of endometriosis. It has got anti-inflammatory and antiangiogenic activity.

Gonadotropin-releasing Hormones Agonists (GnRHa)

Gonadotropin-releasing hormones agonists has been used to treat endometriosis over the last 20 years.[62] They are chemically similar, generally well-tolerated, safe, and effective when used with add-back medication.[63] Use of it help to protect fertility, halt disease progression if the disease is diagnosed early, or prevent recurrent endometriosis. Gonadotropin-releasing hormones agonists is an option for endometriosis with symptoms that remain after first-line treatment. They stop estrogen production in several ways when used for more than 2 weeks. Symptoms usually improve 4–8 weeks after the start; however, in some women, symptoms temporarily worsen in the first 2 weeks. Ovulation and menstruation might return after a variable period of withdrawal of GnRHa.

According to the CNGOF and SOGC, GnRHa with add-back therapy may be continued for up to a year but no more than 6 months. ESHRE cautions that additional analysis is required to establish the duration of the therapy, as mentioned earlier. In Germany, add-back therapy (5 mg of norethisterone per day) has been approved for a 12-month course. However, GnRHa is not recommended as a treatment for ovarian endometriomas by the German Society (S2k).[64] Before age 18,[65] GnRHa should not be started for pelvic discomfort. And to guarantee that the majority of bone accretion occurs in cases of medically proven endometriosis, GnRHa should be delayed until age 16.[65,66]

Gonadotropin-releasing Hormones (GnRH) Antagonists

GnRH antagonist is a promising drug in treating endometriosis, especially endometriosis-associated pain. Without an adverse reaction, it limits the release of ovarian steroid hormones and suppresses ovarian function dose-dependently. The key benefits of GnRH antagonists are the oral route of administration, immediate suppression of the release of FSH and LH, and individualized tailoring according to the patient's symptoms and preferences.[67,68] As it causes dose-dependent estrogen suppression, the hormone release is quickly reversible and returns to normal at the end of the treatment. The FDA has already approved two oral GnRH antagonists (elagolix and relugolix); linzagolix is the third to become available.[69] But currently, only four guidelines (ESHRE, ASRM, CNGOF, and WES) recommend its use. However, they supported that evidence is insufficient to conclude the verdict for use in endometriosis-associated pain. In women with moderate-to-severe endometriosis-related pain, elagolix dramatically improves fatigue levels, according to results of phase III randomized, double-blind, multicenter, placebo-controlled trials.[70] Elagolix considerably lessens dysmenorrhea and intermenstrual pelvic pain when

taken at doses of 150 mg daily and 200 mg BID, respectively.[71] The recommended duration of treatment is 6 months. Due to the dose-dependent reduction of estrogen, add-back therapy may be needed. 46–63% of those who get elagolix monotherapy and 19–27% of people who receive hormone add-back experience side effects such as hot flushes.[72] Patients using elagolix 150 mg once daily and 200 mg twice daily were shown to have decreased BMD in 0.3%, 3.6%, and 0.2% of instances, respectively.[73]

Aromatase Inhibitors (AI)

Aromatase inhibitors reduces estrogen synthesis in the ovary, and peripheral tissue as overexpression of aromatase enzyme has been found in the endometriotic deposit.[74,75] According to animal studies, AI effectively removes endometriotic implants and changes peritoneal fluid vascular endothelial growth factor (VEGF).[76] According to a study,[77] letrozole affects endometriosis-related discomfort comparable to oral contraceptive tablets. There is a possibility of developing a cyst if letrozole is given alone. So, it gives better results when combined with progestin NETA as add-back therapy. This combination therapy protects from hypoestrogenic symptoms and causes a 75% reduction of endometrioma volume and improved pain symptoms after three months of treatment.[78]

It also could be used with OCPs, or GnRHa to avoid ovarian stimulation. When used with GnRHa, it improves pregnancy outcomes in the IVF cycle.[79] Moreover, compared with postoperative treatment with GnRHa or danazol, it significantly lowers the incidence of endometriosis recurrence, whether administered alone or in conjunction with GnRHa.[80]

Cabergoline

Endometriosis must undergo neo-angiogenesis to begin, grow, develop, invade, and recur. Angiogenesis and concurrent neurogenesis significantly influence the development of endometriotic implants and subsequent pain.[81,82] Several antiangiogenic drugs have been investigated as possible endometriosis therapies. Cabergoline-a dopamine receptor 2 (DRD2) agonist, has antiangiogenic properties. In a mouse model, cabergoline was reported to reduce angiogenesis.[83] It does not impede healthy fetal development or pregnancy advancement and has a tolerable safety profile.[84,85] It is a drug that has no antipregnancy effect like others. In pilot research involving nine surgically diagnosed endometriosis patients, cabergoline (0.5 mg twice/week for 6 months) was an effective treatment option for endometriosis-related chronic pain and a VEGF inhibitor.[86] When used cabergoline with dienogest, endometriotic implants are significantly reduced compared with dienogest or cabergoline alone, as depicted in a mouse model.[87]

Modified surgical approach: Surgery in the form of cystectomy causes significant follicular loss due to (i) excision of the cyst wall and healthy tissue together and (ii) electrocauterization to control bleeding. Loss of the follicular pool is directly related to the cyst's size and laterality. If a cyst is bilateral and bigger, there is a chance of ovarian failure or significant loss of follicles. Therefore, preoperative assessment by AMH is essential in endometriosis. To avoid surgical damage, scientists recommended different modalities of surgery, which can save the follicular pool. These include

Surgical Technique

- Combined ablation and cystectomy: Donnez et al. created a surgical procedure that combines cystectomy with CO_2 ablation. A cystectomy is performed, which involves removing 80–90% of the cyst and then using a laser to burn away the remaining cyst wall. The risk from cystectomy and recurrence from ablation alone was decreased by this method. The study shows low recurrence and maintained the volume of the ovary and AFC.[88]
- Three-stage technique cystectomy for a big cyst (> 5 cm): It entails a second laparoscopic treatment after GnRHa suppression for 3 months, followed by laparoscopic cyst drainage and biopsy. The cyst wall is vaporized during a cystectomy using CO_2, bipolar diathermy, or plasma ablation. Since less heat damage is done to normal ovarian tissue, this combination approach may be preferable to cystectomy. Compared with the three-stage group, where the drop was from 4.5 to 3.99 ng/mL, the mean serum AMH level in the conventional group was much lower, going from 3.9 to 2.9 ng/mL. The traditional group experienced a considerably greater fall in AMH following surgery than the three-stage group (25.64% vs 11.33%, respectively).[89] The length of time needed before IVF is the three-stage method's drawback.
- Endometrioma vaporization: After cystectomy or bipolar current forceps vaporization of unilateral or bilateral endometriomas, AMH levels decline. In both situations, the OR decreases, particularly in people with severe endometriosis or over 38. The difference was statistically significant for patients with bilateral endometriomas. However, postoperative AMH drop was greater following cystectomy than after vaporization.

  AMH levels dropped after the bilateral cystectomy, going from 3.1 to ± 1.7 ng/mL before surgery to 0.8 to ± 0.7 ng 1 year later. In contrast, the preoperative AMH levels for the bilateral vaporization group were 2.7 ± 1.8 ng/mL and fell to 1.3 ± 1.5 ng/mL 1 year after surgery.[90]

  Another multicenter randomized clinical trial compared the changes in AMH and AFC following cystectomy or CO_2 laser vaporization and discovered that 3 months after surgery, there was a significant decrease in serum AMH in the subjects treated with cystectomy (from 2.6 ± 1.4 to 1.8 ± 0.8 ng/mL; 95% CI: 1–0.2; $p = 0.09$), but no significant reduction was found in the group treated with laser vaporization (from 2.3 ± 1.1 to 1.9 ± 0.9 ng/mL; 95% CI: 1–0.2; $p = 0.09$).[91]
- Laparoscopic cyst aspiration and sclerotherapy: Sclerotherapy is used mainly in varicose veins to shrink the vessels where a sclerosing agent is injected into the vein. Following the same concept, sclerosing agent can be used in the decompressed endometriotic cyst to collapse the cyst walls by an inflammatory reaction. Tetracycline, methotrexate (MTX), and ethanol are utilized as sclerosing agents. The sclerosing agent is injected into the cyst cavity following aspiration, and after a thorough washing of the cyst walls, after a short period, it is withdrawn. That induces an inflammatory reaction and causes scarring and collapse of the cyst. AMH fall is nil as the cyst wall is kept in place.

  The 10 steps outlined by Crestani et al. can be used to provide ethanol sclerotherapy for an endometrioma.[92] After excluding malignancy by MRI, laparoscopic cyst aspiration followed by cleaning the cyst cavity with ringer's lactate solution and exposure of the cyst walls to ethanol for 10–15 minutes was done. The peritoneal cavity was explored to exclude peritoneal carcinogenesis, and finally, tissue was taken for histopathology.

  De Cicco Nardone et al. treated 54 patients with ethanol sclerotherapy after cyst aspiration instead of cystectomy, even in bilateral endometrioma and associated deep endometriosis, and found a <10% recurrence. Within 36 months of the follow-up period, only 5 (9%) patients had a recurrence, and

the overall pregnancy rate was 57%.[93] The group had no major complications.

- Hemostatic technique: There is a significant loss of follicles after cauterization of the cyst wall, and if hemostasis can be done without cauterization OR could be saved.

  Following are the different ways to control bleeding without cauterization.

- Cystectomy with vasopressin: To prevent the probable loss of ovarian reserve, Saeki et al. suggested vasopressin as a helpful method in treating endometriomas.[94] Vasopressin dissolved in saline can help prevent coagulation-induced follicular loss by lowering the bipolar coagulation required for hemostasis. Also, because the vasopressin injection enhances the ability to see the cleavage plane between the cyst and the ovary, it lessens inadvertent tissue loss during cystectomy.
- Hemostatic Sealant (Gelatine–thrombin Matrix Seal, FloSeal): Hemostatic sealant can be applied to stop bleeding during surgery. AMH did not significantly decrease compared with the diathermy group during the follow-up period. The recurrence rate varied significantly between the sealant and diathermy groups, 7.7% vs. 22.2%, respectively ($p = 0.060$).[95]
- Surgicel (oxidized regenerated cellulose-Ethicon): The use of surgery for hemostasis can save ovarian reserve. In a randomized controlled trial, two hundred women were treated by four treatment modalities: only drainage, cystectomy, drainage and surgical, cystectomy, and surgical to monitor the rate of recurrence and the effect of therapy on the OR. The decline in AMH was lowest in the drainage and surgical group compared with the other three groups. After a 2-year follow-up, the cystectomy and the surgical group had a considerably reduced recurrence rate than the other groups ($p = 0.004$).[96]
- Suturing: OR can be saved with careful suturing to control ovarian hemorrhage. Suturing had a less significant effect on postoperative AMH levels than ultrasonic energy and intra-ovarian hemostatic sealants, according to a recent comprehensive review and meta-analysis.[97] A prior meta-analysis comparing bipolar coagulation and suture concluded that bipolar coagulation caused more damage to the ovarian reserve than the suture during ovarian hemostasis following cystectomy.[98]

Alternate to Surgery

Transvaginal Aspiration with Sclerotherapy

Ethanol sclerotherapy: One intriguing method of treating endometrioma is ultrasound-guided noninvasive transvaginal aspiration followed by injecting 95% alcohol (Ethanol) into the cyst cavity. By dissolving the cyst wall through a chemical reaction, sclerosing agents stop the cyst from growing again. The combination of cytotoxic damage, hypertonic cell dehydration, coagulation, and thrombosis in the presence of blood components makes up the mechanism of action of ethanol sclerotherapy.[99]

It takes about 20–30 minutes and is less intrusive than laparoscopic surgery. A sclerosing agent is less likely to harm functional ovarian tissue, which lowers the likelihood that the OR would be depleted. If the sclerosing agent is removed after 10 minutes and the pelvic area is washed with normal saline, complications, such as infection, internal bleeding, irritation from the agent, and adhesion are less likely to develop.

According to a study, the sclerotherapy group had superior OR and stimulation response than the untreated group. Moreover, compared with the non-aspiration group, the rate of pregnancy and continued pregnancy was greater in the ethanol aspiration group (48.3% against 19.2%, $p = 0.04$; and 55.2% vs 26.9%, $p = 0.03$, respectively).[100]

According to a systematic review, the rate of endometrioma recurrence following sclerotherapy ranged from 0 to 62.5%. It was discovered that women receiving sclerotherapy with prolonged ethanol washing (ethanol instillation time >10 min) have a lower recurrence rate. There was no change in the pregnancy rates even though more oocytes were recovered during IVF procedures following endometrioma sclerotherapy than laparoscopic cystectomy. The number of recovered oocytes and the clinical pregnancy rates between the sclerotherapy-treated and the control groups were comparable.[101] In one study, when the duration of the ethanol instillation was less than 10 minutes, the recurrence rate was 62.5%, and when it was greater than 10 minutes, it was 9.1% (P.001).[102]

According to another systematic review, the recurrence rate was considerably lower with sclerotherapy lasting longer than 10 minutes than with shorter treatments (OR, 0.2; $p = 0.015$). It was found that sclerotherapy enhanced the pregnancy rate compared with surgery after recurrent endometrioma (OR, 2.0; $p = 0.042$).[103]

According to Jose et al. comparisons of the outcomes of surgery and alcohol sclerotherapy, the latter protects OR and fertility in endometrioma patients more effectively than the former. After sclerotherapy, there were notable increases in blood estradiol concentrations, AFC recovery, and pregnancies.[104]

An observational study with 53 patients showed a recurrence rate of 20.75%, 4 of which needed re-aspiration. Among patients who received further treatment, 16.57% got pregnant by IUI, and 31.71% got pregnant by ART -no complications developed.[105]

No major complications were observed in any study.[100–105]

Methotrexate sclerotherapy: A folate antagonist called MTX is thought to inhibit cells in the endometrioma cyst wall by blocking DNA synthesis. The recurrence rate of endometrioma treated with aspiration alone and aspiration combined with MTX sclerotherapy was examined in an RCT. After three treatment cycles, there was a significantly lower rate of cyst persistence in the aspiration and MTX group (14%) compared with the aspiration-only group (45.3%).[106] A case-control study with unilateral endometriomas revealed no difference in the AFC, the number of oocytes extracted, the rate of fertilization, or the embryo quality between the MTX-treated ovary and the contralateral ovary that was unaffected. The findings showed that MTX had no detrimental effects on oocyte quality or subsequent pregnancy outcomes. Around one-third of the amount used for ectopic pregnancy—30 mg of MTX—is diluted in 3 mL of regular saline as sclerotherapy for endometrioma. The safety factor could be the decreased MTX dose. Of the 65 women who used MTX and underwent ART, 21 became pregnant, and 14 of those pregnancies ended in live births with no congenital disabilities.[107] These findings further support the idea that a low dose of MTX is a reasonable therapeutic option. This method's delay of 3 months before beginning COH for IVF therapy is a pitfall of this drug.

Tetracycline sclerotherapy: Tetracycline sclerotherapy is another safe alternative to surgery. About 5–10 mL of 5% tetracycline is used as sclerotherapy. Jeffry et al. reported that cysts were resolved completely in 75% of cases. Before complete resolution, 8 out of

24 patients needed repeat aspiration of watery fluid. Two patients required repeat tetracycline treatments, and one showed no improvement. And 57% of patients who had IVF became pregnant. It could be concluded that sclerotherapy using 5% tetracycline is a quick, efficient substitute for surgery to treat endometriomas before IVF.[108]

Approaches to reduced time to live birth: As endometriosis affects fertility, especially OR reduced; so, it is logical to approach the treatment which needs the least time to get pregnant. Also, in endometriosis, the quality of oocytes is altered due to the toxic pelvic environment. Oocytes that ovulate *in vivo*, if exposed even for a transient moment to the pelvic cavity's toxic characteristics, get altered in quality.[109] That explains why endometriosis-affected women have lower natural conception odds. Eliminating toxic endometriotic foci boosts the pregnancy rate immediately following surgery, increasing the likelihood of getting pregnant within 6 months of the procedure.[109–111] According to numerous studies,[112–114] pelvic endometriosis surgery doubled the likelihood of spontaneously becoming pregnant within 18 months of the procedure. Vercellini et al. reported a 50% chance of getting pregnant within 18 months of surgery.[112] But before considering surgery, it is important to assess the possibility of natural conception concerning the severity of the disease, quality of sperm, and OR for setting aside 12–18 months to allow for spontaneous conception. Possible benefits from surgery should be assessed beforehand, not during the surgical procedure,[115] as surgery may further reduce the fertility potential. Surgery should only be considered when all other parameters for fertility are normal, and women are in their 20s.

The procedure may harm their reproductive prospects and delay management by anticipating natural conception 12–18 months following surgery. And they must not be allowed for natural conception for more than 18 months. But for women who are in their 30s, ART should be the first approach.[116]

ART has the added benefit of overcoming implantation's negative effects in endometriotic patients. The eutopic endometrium exhibits several cellular and molecular abnormalities that favor higher production of estrogen, cytokines, prostaglandins, and metalloproteinases,[117] according to a rigorous study of the subject by Bulun et al.[118] *In vitro* studies show that these increased estrogen, cytokines, prostaglandins, and metalloproteinases are responsible for improperly transforming decidualized cells.[119] Estrogen production increased, and there was an altered ratio of estrogen receptors α and β. Estrogen receptor β becomes 142 times higher, and receptor α becomes nine times lower than normal endometrium,[120] which prevents the progesterone receptor gene from being activated.[121] Hence, it has been asserted that the changes to the eutopic endometrium change the endometrial receptivity to embryo implantation, even in ART.[122,123] Yet, there is a chance to deal with the issue in ART by freezing everything and delaying embryo transfer in a new cycle. Subsequently, frozen embryo transfer is done after preparing endometrium by suppressing ovarian function and using exogenous estrogen progesterone. By inhibiting the local generation of estradiol (E2)[124] and reducing progesterone resistance,[125] ovarian suppression by hormone therapy appears to restore the effects of endometriosis on the eutopic endometrium notably.[126] According to research, the ovarian suppression from the progesterone and E2 therapies used to timing frozen embryo transfers have a similar positive impact.[127,128]

Fertility preservation: Reproductive tissue freezing with fertility preservation has been widely used as standard care for cancer survivor women. Due to damage of gonadal tissue by chemo and radiotherapy, many patients may undergo premature ovarian failure (POF). Tissue freezing for fertility preservation is common practice for cancer patients. Endometriosis is a benign condition, and no chemoradiotherapy is required; they may require tissue freezing as early ovarian failure is possible—or significant falling of AMH. Endometriosis is a recurrent disease and may need repeated surgery when all efforts of medical treatment fail to relieve the severe symptoms. In such circumstances, recurrent ovarian surgeries may do irreparable ovary harm.[129,130] Fertility preservation is the option in such cases. Not only repeat surgery, but sometimes the 1st, surgery may also cause ovarian failure when endometriomas are multiple, big, and bilateral or the pre-surgical AMH level is too low. These patients also are candidates for reproductive tissue freezing. There is insufficient information regarding the preservation of fertility in endometriosis patients.[131] The year 2009 saw the publication of the first case study with oocyte cryopreservation for endometriosis.[132]

Forty-nine individuals had COH to preserve their fertility, according to Raad et al. Most individuals had endometriomas or deep infiltrating endometriosis (DIE). The authors propose that in some individuals, COH may be considered before endometrioma excision because the responsiveness to COH is markedly diminished following surgery.[133,134]

Preservation can be done in the oocyte, embryo, and ovarian tissue. Unmarried girls are the candidates for oocyte preservation. Only married women can freeze embryos. Irrespective of marital condition, ovarian tissue can be frozen after collecting tissue during surgery when COH cannot be given due to a severe symptom of the patient who needs an oophorectomy or refuses to undergo COH.

Women should be advised very clearly regarding oocyte cryopreservation that success rates vary greatly depending on age and that fertility preservation does not ensure conception. According to data, the live birth rate varies according to the woman's age at COH, from 7.4% for those under 30 to 5% for those over 38. Nevertheless, a recent retrospective analysis from 2021 by Leung et al. demonstrates no difference in the live birth rate per transfer (48.5% for those under 38 and 28.6% for those over 38). No successful pregnancies happened when patients used planned OC under 40 years old.[135]

It is advised that women under the age of 38 cryopreserve 15–20 oocytes, while those between the ages of 38 and 40 should suggest 25–30 oocytes.[136]

Doyle contrasted the results of the intended vitrified oocyte with those of a fresh oocyte. He demonstrated that the vitrified oocyte group and the fresh oocyte group had comparable rates of fertilization (69.5 vs 71.7%, $p > 0.05$) and ongoing pregnancy (38.6 vs 36%, $p > 0.05$).[134]

A multicenter study is required to establish the use of oocyte cryopreservation in endometriotic patients. Because the technology may not be productive as a high number of oocytes may not be available in women with decreased OR. Also, oocyte quality is compromised in women with endometriotic patients, which makes oocyte cryopreservation fail.[137]

Ovarian cortical tissue freezing from an ovary with a 9 cm endometrioma was initially described by Donnez et al. in 2005.[138] Despite being unable to conceive naturally, the patient gave birth after three IVF cycles.[138] According to data from various centers, the live birth and clinical pregnancy rates for women receiving gonadotrophin therapies following ovarian tissue cryopreservation are equal to those after oocyte cryopreservation.[139]

There is still debate over whether some endometriosis patients need this technology or none due to the scarcity of information on the results, use, and cost-effectiveness of fertility preservation.

Hence, fertility preservation may benefit women at risk for ovarian insufficiency or failure due to conditions like bilateral ovarian endometrioma or a history of unilateral cystectomy with contralateral recurrence.

Conclusion

Endometriosis is a lifelong disabling condition. Its effects could begin from adolescence and continue long after menopause. If a woman does not receive the right medical care over this prolonged period of pain, it could worsen her condition than cancer. The most significant complication of endometriosis is infertility. The tubo-ovarian relationship was impaired as the disease advanced, and the ovary became the target organ of its destruction. Also, it could render the endometrium incapable of receiving the embryo. Because of the pain and tissue damage, even the couple's relationship puts the couple's ability to conceive normally in jeopardy. Women with endometriosis, therefore, need to begin receiving therapy as soon as appropriate. The major goal of care is to stop the course of the disease, and if that is not possible, to assist women in becoming mothers through ART or ovarian tissue preservation for later use. Whatever the strategy, at the end of the day, motherhood makes a woman's life right and joyful when the illness is diagnosed in time and treated with the appropriate modalities.

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