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"FERTILITY PRESERVATION STRATEGIES IN WOMEN WITH ENDOMETRIOSIS"

Himanshi Pareek[1], Satpal Kushwaha*[2], Tanya Sharma[3], Ranjan Kumar Singh[4]

[1]Student of Faculty of Pharmaceutical Sciences, Mewar University, Gangrar, Chittorgarh, Rajasthan, India - 312901.

[2]Assistant Professor, Faculty of Pharmaceutical Sciences, Mewar University, Gangrar, Chittorgarh, Rajasthan, India - 312901.

[3]HOD, Assistant Professor Faculty of Pharmaceutical Sciences, Mewar University, Gangrar, Chittorgarh, Rajasthan, India - 312901.

[4]Associate Professor Faculty of Pharmaceutical Sciences, Mewar University, Gangrar, Chittorgarh, Rajasthan, India - 312901.

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***Corresponding Author: Satpal Kushwaha**
Assistant Professor, Faculty of Pharmaceutical Sciences, Mewar University, Gangrar, Chittorgarh, Rajasthan, India - 312901.
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ABSTRACT

Endometriosis is a chronic, estrogen-dependent inflammatory disorder that affects reproductive-aged women and is frequently associated with diminished ovarian reserve and infertility. Fertility preservation has become an essential component of management, particularly for patients who delay childbearing or require surgical intervention that may compromise ovarian function. This article reviews current fertility preservation strategies in patients with endometriosis, including oocyte and embryo cryopreservation, ovarian tissue cryopreservation, and the role of medical and surgical approaches in optimizing reproductive outcomes. The impact of endometriotic cysts and repeated ovarian surgeries on ovarian reserve is critically examined, alongside the timing of intervention and patient selection criteria. Emerging techniques and individualized treatment planning are emphasized to maximize success rates while minimizing disease progression. A multidisciplinary approach involving reproductive specialists, gynecologic surgeons, and patients is crucial for informed decision-making. Early counseling and proactive fertility preservation can significantly improve reproductive potential and quality of life in women with endometriosis.

KEYWORDS: Endometriosis; Fertility preservation; Oocyte cryopreservation; Embryo freezing; Ovarian reserve; Assisted reproductive technology (ART); Ovarian tissue cryopreservation; Reproductive health; Infertility; Women's health, etc.

INTRODUCTION

The presence of endometrial tissue outside of the uterus is known as endometriosis. It has been linked to infertility, dysmenorrhea, dyspareunia, and persistent discomfort and may affect the ovaries, fallopian tubes, and pelvic. Although there is ample evidence in the literature linking endometriosis to infertility, the exact cause-and-effect relationship is still up for debate. (1) Infertility and pelvic discomfort are the main symptoms of endometriosis, a chronic, estrogen-dependent illness that mostly affects women of reproductive age. It is distinguished by an inflammatory process that takes place in locations outside the endometrial and myometrial regions that contain epithelial and/or stromal endometrial-like tissue. (2) The ability to cryopreserve oocytes, embryos, and ovarian cortex has made it possible for women whose reproductive potential and ovarian reserve are in danger to maintain their fertility. (3) Endometriotic lesions have various aspects and degrees of the extent of their severity.

Since 1979, classifications have been proposed for the purpose of describing the stage of pathology. However, these classification systems did not provide an adequate prognosis on the reproductive aspect (American Fertility Society (AFS), American Society for Reproductive Medicine (ASRM)). (4)

Briefly, after menses, the patients were administered oral estradiol vale rate (Progynova, 6 mg/day; Schering) starting on days 2–3 of their menstrual periods. Approximately 10 days after initiating oral estradiol vale rate, the serum estradiol (E2) levels and endometrial thickness were measured. Administration of micronized vaginal progesterone (800 mg/day, vaginally, Progeffik; Effik Laboratories) was initiated 3 days before embryo transfer for day-3 embryo transfers. (5)

FERTILITY IN ENDOMETRIOSIS

Endometriosis and fertility Endometriosis-related infertility is thought to be caused by a number of factors, including altered pelvic anatomy, alterations brought on by inflammation, and decreased endometrial receptivity. Folliculogenesis, fertilization, implantation, or a combination of these crucial reproductive processes may be hampered by these changes (Rangi et al., 2023). Given how endometriosis affects ovarian reserve, fertility preservation

might be a beneficial choice for afflicted women. By retrieving and cryopreserving oocytes or embryos, fertility preservation gives women the chance to eventually have biological children. From the first groundbreaking study by Elizur et al. (2009), which described a patient with advanced endometriosis receiving fertility preservation treatment. (6)

Ovarian stimulation for fertility preservation in women with endometriosis COS

The same procedures used in traditional assisted reproductive technology are used in COS for FP

these procedures have already been shown to be safe for endometriosis-affected women, particularly if a freeze-all technique with delayed embryo transfer is selected. Although using the antagonist GnRH stimulation protocol is linked to a marginally increased number of retrieved oocytes, no particular COS strategy is advised for FP in women with endometriosis. GnRH triggering is possible if an antagonist stimulation regimen is utilized. Compared to HCG triggers, this enables a decrease in the frequency of ovarian hyper stimulation syndrome and a reduction in discomfort sensations. There is not enough information to conclude if women should stop hormonal treatments before to stimulation in order to improve the quality of the oocytes they rec e and the outcomes of their pregnancies. Progestin (like dienogest) or a GnRH antagonist are typically used as pretreatment prior to IVF; neither has been shown to be clearly superior to the other. The number of retrieved oocytes and the reaction to GnRH agonist triggers during the IVF cycle may be reduced by hormonal medications that alleviate pain in women with endometriosis, according to some authors. (7)

THE MAGNITUDE OF SURGERY'S IMPACT ON OVARIAN RESERVE IS UNPREDICTABLE

Since research on this subject has produced conflicting results, it is uncertain if preoperative serum AMH levels are relevant in predicting the possibility of achieving pregnancy or the necessity for fertility preservation. Age, preoperative serum AMH level, endometriomas diameter and laterality, unicystic or multicystic display, pelvic anatomy and adhesions, surgical skills, techniques, and complexity, hemostasis methods, and prior surgery are some of the composite and interrelated factors that may influence oocyte preservation counseling for women with ovarian endometriosis. Certain aspects could be easily evaluated prior to surgery, but others might not.

Although statistically significant reductions in blood AMH levels are indicative of a loss in functional ovarian reserve after endometriotic cystectomy, there appears to be a wide

variation in AMH reduction among individual-operated women. While some women may show a slight drop in serum AMH levels, others may show a significant decline. The degree of the drop in serum AMH is frequently variable. Due to the numerous interconnected measurable and non-measurable variables, it is currently impossible to forecast individual AMH reduction. (8)

AVAILABLE FERTILITY PRESERVATION STRATEGIES

- **OOCYTE CRYOPRESERVATION**

Pretreatment before to IVF: There is not enough information to say if women should stop taking hormonal treatments prior to the stimulation in order to improve the quality of the oocytes they receive and the outcome of their pregnancy. Pretreatment before to IVF usually consists of either a GnRH antagonist or a progestin (such dienogest), with neither clearly superior to the other.

COS procedure: Although the GnRH antagonist protocol is linked to a marginally increased number of recovered oocytes, no one is advised. (9) The process of freezing and preserving oocytes at low temperatures is known as oocyte cryopreservation. When the patient decides to pursue a reproductive goal, these frozen oocytes may be used. This technique, which was first created for patients receiving gonadotoxic treatments, has been used for social freezing and FP in endometriosis-affected women. (10)

- **OVARIAN TISSUE CRYOPRESERVATION**

For FP in cancer patients who must start high-risk gonadotoxic treatments (chemotherapy or radiation) and are unable to postpone treatment in order to undergo COS, ovarian tissue cryopreservation (OTCP) is used. In addition to those with cancer, OTCP benefits women and girls with benign diseases like β-thalassemia and autoimmune disorders that require bone marrow transplantation, as well as benign ovarian conditions like endometriosis that require procedures like oophorectomy with a risk of premature ovarian insufficiency. For individuals who need urgent surgery but are unable to undergo COS due to conditions such hydronephrosis or occlusive bowel endometriosis, OTCP may be a useful alternative. Two surgical operations are necessary for OTCP: the first is to remove the ovarian tissue, and the second is to transplant it. Furthermore, compared to oocyte or embryo cryopreservation, it has a greater morbidity rate, damages ovarian reserve, and may encourage the formation of adhesions following surgery. Usually, the surgery involves either a full oophorectomy or the surgical excision of ovarian cortical tissue from a portion of the ovary. Following collection,

the cortical tissue is divided into thin, 0.5 × 1 cm2 strips that are 1-2 mm thick and cryopreserved for later transplantation. Primordial follicles show comparatively greater resilience since they are situated in a less vascularized environment. After thawing, endocrine function and the potential for spontaneous conception can be restored by transplanting the ovarian cortical strips into orthotropic places (such as the atrophic ovary). As an alternative, they can be transplanted into heterotopic locations (such the abdomen wall's subcutaneous region), which will likewise restore endocrine function. Patients with endometriomas may also be able to obtain ovarian tissue for cryopreservation by removing the tissue that surrounds these benign cysts. Different numbers of follicles might be lost following surgical excision of the endometriomas cyst wall. The number of follicles in histological sections of the cyst wall is correlated with the age of the patient; the endometriomas wall has more follicles in younger patients. (11)

- **OVARIAN RESERVE**

The most frequent site of endometriosis is the ovary. One of the primary predictors of fertility is ovarian reserve, which is largely correlated with a woman's age. The quantity of non-growing, unrecruited primordial follicles is known as ovarian reserve at this time, there is no clinical technique that can reliably predict ovarian reserve. Antral follicle count (AFC) and serum anti-Mullerian hormone levels (AMH) are now the most often used markers of ovarian function, despite questions about their usefulness and specificity in clinical practice. In the context of assisted reproductive technologies (ART), AMH is most useful in identifying women who would not react well to gonadotropin stimulation. AMH concentrations can be measured at any time because they are not significantly impacted by oral contraceptives or the menstrual cycle. The pathophysiologic mechanism behind endometriosis's decreased ovarian reserve is yet unknown. However, there is mounting genetic, histological, and morphological evidence that endometriomas negatively impact ovarian activity. It is uncertain if the endometriomas decreases the amount of functional tissue accessible by a direct toxic impact or a space-occupying effect (mechanical stretching damage). An endometriomas is an unusual benign cyst that lacks a true capsule; as a result, the contents of the cyst are exchanged with the nearby healthy ovarian cortex. Unlike other benign cysts, endometriotic cyst fluid might possibly harm healthy tissue by causing oxidative stress in living cells. High levels of free iron, which can facilitate the generation of reactive oxygen species (ROS) that are highly diffusible between cellular compartments, were found in the cystic fluid using molecular comparison analysis. Compared to the contralateral healthy

ovary, follicles in touch with the endometriomas had higher iron concentrations in their follicular fluid. (12)

OOCYTE QUALITY, EMBRYO TRANSPORT, SPERM FUNCTION AND MOTILITY, SPERM OOCYTE INTERACTION

Studies on the effect of endometriosis on ovulation have produced conflicting findings. For example, a 2009 research by Somigliana et al. discovered that ovulation was statistically significantly reduced in women with monolateral endometriomas, occurring in just 31% of afflicted ovaries compared to an expected 50% in healthy ovaries. However, there was no discernible difference in ovulation rates between afflicted ovaries (50.3%) and healthy ovaries (49.7%) in a larger prospective research that tracked 244 women over 1199 cycles. Despite these results, there is still little and conflicting clinical data about the frequencies of spontaneous ovulation in endometriosis-affected women. Luteinized unruptured follicle syndrome, in which the dominant follicle fails, and hyperprolactinemia, which interferes with luteinizing hormone pulsatility and hypothalamic function. The effects of endometriosis on the quality of oocytes and embryos are still complicated and not entirely understood. The overall impact on embryo quality is unclear, despite research showing that oocytes from women with endometriosis may show altered shape, reduced cytoplasmic mitochondrial content, and in vitro maturation failure. (13)

IMPACT OF SURGICAL APPROACHES ON OVARIAN RESERVE AND FERTILITY PRESERVATION IN ENDOMETRIOSIS MANAGEMENT

The potential benefit of removing an endometriomas to improve fertility must be weighed against the danger of harming the ovarian reserve, as reported by many authors (Dunselman et al., 2014). AMH levels really drop following endometriomas excision, according to several studies and meta-analyses. Additionally, there is a 2.4–13% chance of early ovarian failure following an ovarian cystectomy.

Prior to treatment, AMH levels were considerably lower in those with advanced age, increased BMI, shorter menstrual cycles, bilateral ovarian cysts, advanced surgical staging, or a fully contained Douglas pouch than in those without these symptoms. Furthermore, after a year after laparoscopic cystectomy, AMH levels continued to drop. The excessive removal of healthy ovarian tissue, vascular damage from electrocoagulation, and autoimmune reactions brought on by severe local inflammation are some of the mechanisms that have been suggested as contributing to surgery-related damage to the ovarian parenchyma. Cystectomy

by stripping is one of the methods commonly used in conservative surgical treatment of ovarian endometriomas.

Draining the endometriomas is the first step in the cystectomy by stripping procedure. Next, the cyst wall is carefully separated from the ovarian cortex using mild traction and counter-traction. After that, hemostasis is attained at the cyst bed, frequently with the use of hemostatic drugs, sutures, or bipolar diathermy. When cystectomy is performed for ovarian endometriomas, both the suture approach and hemostatic drugs may be more beneficial in preserving ovarian reserve than the bipolar coagulation method. The ovarian endometriomas cyst wall is destroyed when the cyst is fenestrated, drained, and cleaned out using ablative procedures. Laser and plasma energy provide a more surface-level, tissue-conserving impact than bipolar diathermy. (14)

UNIQUE CHALLENGES POSED BY ENDOMETRIOSIS IN FERTILITY PRESERVATION

Because endometriosis patients have a lower ovarian reserve and lower-quality oocytes and embryos, maintaining fertility might be difficult for them. Ovarian endometriomas are known to mechanically stretch the ovarian cortex and cause inflammatory-mediated damage, which can negatively impact ovarian reserve. When compared to an unaffected ovary, the histologic study of afflicted ovaries shows increased atresia, decreased follicular density, and higher primordial follicle activity.

Women with endometriomas had lower baseline AMH levels than healthy controls, which reflects the detrimental impact of endometriomas on ovarian reserve. Furthermore, women with bilateral endometriomas see a greater decrease in AMH levels than those with unilateral endometriomas. It's unclear, though, what these findings mean clinically. Despite a worse response to gonadotropins and lower oocyte yields, women with endometriomas undergoing IVF had comparable clinical pregnancy and live birth rates to women without endometriomas. AMH is also a poor predictor of spontaneous conception. (15)

DOES SURGERY RESTORE FERTILITY?

It's a tough question as to whether removing endometriotic lesions (via laparotomy or laparoscopy) would boost a woman's chances of becoming pregnant naturally. This complex is caused by several types of endometriosis and many surgical techniques that are used. The lowering of pelvic inflammation is the basis for the belief that surgery increases the likelihood of spontaneous conception. A randomized trial produced the first results

supporting surgery. In a 36-week follow-up, the trial, which involved 341 women, showed that resection or ablation of visible endometriosis improved conception rates. A meta-analysis that considers these trials and compares the surgical technique (± adhesion) with diagnostic laparoscopy produced further supporting findings. When compared to diagnostic laparoscopy, this meta-analysis showed that laparoscopic surgery improved fertility in cases of minimal and mild endometriosis. (16)

OUTCOMES OF FERTILITY PRESERVATION

Compared to infertile women with other reasons, infertile women with OMAs had much fewer oocytes recovered. When comparing OMA patients 35 years of age or younger to those over 35, the number of recovered oocytes was much greater.(14)

ASSISTED REPROCTIVE TECHNOLOGY

ART was first recommended for tubal factor or severe male factor infertility in situations of endometriosis-related infertility. However, the approach to infertility-related endometriosis has been impacted by the overall tendency to postpone the first delivery, new insights into ultrasound diagnosis, and advancements in ART laboratories. These days, ART plays a crucial role and is one of the preferred methods. Some pertinent concerns were raised by ART in endometriosis-affected infertile women. Understanding how pathology might impact outcomes is one part; the second is the potential for the pathology being treated to deteriorate; and the third is how to combine it with other medical or surgical therapies. (15)

THE ROLE MEDICAL THERAPY IN ENDOMETRIOSIS

The usefulness of medical therapy in treating infertility caused by endometriosis is restricted. Hormonal therapies prevent ovulation, and medicinal therapy does not enhance reproductive results, despite its effectiveness in relieving pain. Although there is conflicting information on adjuvant ovulation suppression, adjuvant hormonal therapy is an inexpensive, low-risk treatment that may significantly improve fertility. Long-term postoperative oral contraceptive usage significantly reduced recurring endometriosis, according to a new meta-analysis involving 965 women. (16)

DIFFERENT HAEMOSTATIC TECHNIQUE

To lessen further ovarian tissue damage, studies have looked into the use of topical hemostatic sealants (i.e., medical devices used to control bleeding and seal tissue or fluid leaks during surgical procedures) following the surgical excision of benign ovarian cysts.

Different hemostatic approaches were linked to a much less decrease in ovarian reserve as compared to bipolar coagulation, according to a meta-analysis on the effects of operations requiring the use of hemostatic sealants on ovarian reserve. (17)

MULTIPLE OVARIAN STIMULATION CYCLES MAY BE NEEDED TO ACHIEVE OPTIMAL RESULTS

Multiple stimulation cycles may be necessary to get an ideal number of oocytes (at least 10) since endometriosis patients have a decreased ovarian reserve. For example, patients with severely impaired reserve vitrified an average of about 4–6 oocytes, whereas reported an average of around 9 vitrified oocytes per patient. (18)

AGES AND OVARIAN RESERVE ARE CRITICAL PREDICTORS OF SUCCESS

Fertility preservation results are mostly determined by age and ovarian reserve. According to, CLBRs decreased with advanced age but rose dramatically with a larger number of cryopreserved oocytes. (19)

CHALLENGES AND LIMITATION

- **Reduced ovarian reserve**

Because of persistent inflammation and ovarian damage, women with endometriosis frequently have reduced ovarian reserve, particularly when endometriomas are present. By unintentionally destroying healthy ovarian tissue, surgical cyst removal might further decrease ovarian reserve.

- **Therapeutic options in fertility preservation**

The amount of time that cryopreserved embryos or unfertilized egg cells can be stored varies significantly between nations. The majority of responding centers (such as Austria, Germany, and Italy) are said to have no time limit, although centers in Portugal (10 years), Belgium (until maternal age 43 years), Sweden (10 years), France, and the UK have time limits. There were some differences in the answers to other questions from other centers within the same nation. (20)

Materials and methods

Included were patients who had their first autologous frozen oocyte thaw, followed by in vitro fertilization (IVF) and trophectoderm biopsy for PGT-A using next-generation sequencing at our facility. Patients who had PGT to detect a specific genetic mutation or structural chromosomal rearrangement, or who had a fresh or frozen transfer of an untested

embryo, were excluded. Additionally, patients who were fertilized with surgically extracted sperm or who used donor oocytes were not allowed to participate. The subjects were compared to 3:1 age-matched controls who had a trophectoderm biopsy for PGT-A at the same time as their first IVF cycle using fresh oocytes. The ratio of euploid, mosaic, and aneuploid embryos between those using frozen and fresh oocytes was the main result. Fertilization rates, blastula ion rates, and ovarian stimulation characteristics were secondary results. (21)

Emerging treatment strategies

By clarifying the cellular and molecular processes of endometriosis-related infertility and assuming that the existing hormonal suppression-based therapy has significant adverse effects rather than improving fertility, finding putative signaling pathways for non-hormonal targets of endometriosis linked to infertility is essential. Non-coding RNAs (ncRNAs) have quickly become significant regulatory molecules in cancer and a number of reproductive disorders, including endometriosis and recurrent pregnancy loss. Although the US FDA has authorized three RNAi treatments, the use of ncRNAs as a therapeutic tool is still in its early stages. (22)

Number of oocytes to freeze and pregnancy outcomes

The number of oocytes needed for cryopreservation is complicated and relies on a number of variables, including the patient's age, the number of children wanted, and the stimulations required to obtain a sufficient number of mature oocytes. Age-related success rates show that the live birth rate per warmed vitrified egg changes with age, ranging from 5% for women over 38 to 7.4% for those under 30 during COS. For a decent chance of success, it is advised that women under the age of 38 cryopreserve 15–20 oocytes, while those between the ages of 38 and 40 should keep 25–30 oocytes. In endometriosis patients, the number may be greater because of possible problems with egg quality.

It's unknown, though, how many stimulation cycles are ideal and if they should be followed by a hormonal treatment period. The quantity of oocytes collected, endometriosis-related discomfort, patient preferences, and related expenses should all be taken into account while answering these questions. (23)

FERTILITY SPARING SURGERY

Reducing possible iatrogenic damage to the ovarian reserve is necessary to maximize fertility in endometriosis patients. In this situation, adnexal sparing surgery plays a critical role in increasing follicle accessibility before ART due to endometriosis-associated infertility in

symptomatic women with endometriosis-associated discomfort. Therefore, to prevent any damage to the healthy parenchyma and ovarian vascular network, competent surgeons with knowledge of reproductive pathophysiology are needed. Regardless ofssss the surgical method, the two primary hazards of endometriomas surgery are decreased normal ovarian cortex (ovarian reserve) and disease recurrence. For endometriomas, a number of surgical techniques have been suggested: Ablative, excisional, or both.(24)

CONCLUSION

In summary, fertility preservation has emerged as an essential component in the comprehensive management of women diagnosed with endometriosis. Given the progressive nature of the disease and its potential to adversely affect ovarian reserve, oocyte quality, and overall reproductive capacity, early counseling and timely intervention are of paramount importance. Various fertility preservation strategies, including oocyte cryopreservation, embryo freezing, and ovarian tissue cryopreservation, provide viable options for women to safeguard their reproductive potential before disease progression or surgical treatment further compromises fertility. Furthermore, the choice of an appropriate preservation technique should be individualized, taking into account factors such as the patient's age, stage and severity of endometriosis, ovarian reserve status, and personal reproductive goals. Advances in assisted reproductive technologies have significantly improved the success rates of these interventions, offering renewed hope to affected individuals. However, careful consideration must also be given to the possible risks, costs, and long-term outcomes associated with these procedures. Importantly, a multidisciplinary approach involving gynecologists, reproductive specialists, and counselors is crucial to ensure optimal decision-making and patient-centered care. Increasing awareness and incorporating fertility preservation discussions into routine clinical practice can empower women to make informed choices about their reproductive future. Overall, integrating these strategies into standard endometriosis management not only enhances fertility outcomes but also contributes positively to the psychological well-being and quality of life of women affected by this condition.

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