Endometriosis-Associated Infertility: Pathogenesis, Surgical and Novel Treatment Options

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***Abstract*—Endometriosis is a chronic disorder of the female reproductive system described primarily by the presence of endometrial glands and stroma outside the uterine cavity (ectopic endometrium) that has pleiotropic direct and indirect effects on reproduction. The prevalence of this condition in women is approximately 6–10% of women of reproductive age who experience endometriosis, while 30–50% of women with endometriosis experience infertility. Stigmata of endometriosis include dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding, and infertility. This review article mainly focuses on the pathogenesis of endometriosis and how it induces infertility, which includes several theories like retrograde menstruation, coelomic metaplasia, altered immunity, stem cell involvement, oxidative stress, hormonal imbalance, etc., and how all these pathological conditions lead to infertility in women. The current article also explores novel, promising non-hormonal therapeutic options as immune checkpoint inhibitors (ICIs), vascular endothelial growth factor (VEGF) antagonists, and stem-cell–based therapies. In certain cases, a combined medical and surgical treatment strategy may provide the most effective management.**

***Index Terms*—Endometriosis, infertility, coelomic metaplasia, retrograde menstruation, altered immunity, stem cell therapy, dysmenorrhea, dyspareunia, VEGF, IVF, IUI, FET**

I. INTRODUCTION

Infertility is one of the leading problems all over the globe. One of the causes of infertility is endometriosis. Endometriosis is a chronic gynaecologic condition that mostly affects 5-15% of women of reproductive age and 3-5% of postmenopausal women (1). Endometriosis is defined by the presence of endometrial tissue outside the uterine cavity, and it can progress to involve multiple organs. Some of the symptoms are seen in endometriosis, like severe pelvic pain, dysmenorrhea, dyspareunia, dyschezia (2), and hematochezia. Some of the theories that explain the pathophysiology of endometriosis-associated infertility are retrograde menstruation, coelomic metaplasia, immune dysregulation, oxidative stress, and stem cell theory, but these theories are still controversial. Endometriosis-associated infertility is a complicated condition that is presently considered multifactorial. (3) The diagnosis of endometriosis is established by the presence of endometrial lesions in the peritoneal cavity.

This review mainly focuses on how the pathophysiology leads to endometriosis-associated infertility, and this review article covers the surgical treatment options and novel treatment strategies for the treatment of endometriosis associated with infertility.

II. PATHOGENESIS OF ENDOMETRIOSIS AND ASSOCIATED INFERTILITY

Understanding the pathogenesis of endometriosis is crucial, given its significant clinical and therapeutic implications. Despite extensive research, no single theory fully explains the natural history of the disease or accounts for its varied clinical presentations. Here, we review some pathophysiological pathways involved in endometriosis, which ultimately lead to infertility in women.

III. RETROGRADEMENSTRUATION

The most widely accepted theory explaining the pathogenesis of endometriosis is the retrograde menstruation theory, first proposed by Sampson in the 1920s. According to this theory, during menstruation, the endometrial lining is normally shed and expelled through the vagina; however, in some individuals,

viable endometrial cells flow backwards through the fallopian tubes into the pelvic cavity and ovaries. These refluxed endometrial fragments may subsequently adhere to the ovaries, fallopian tubes, or other pelvic organs, leading to the formation of ectopic endometrial tissue outside its normal physiological location. Although retrograde menstruation is a common phenomenon, only approximately 6–10% of individuals develop endometriosis, suggesting that additional factors contribute to disease establishment (4). Under normal conditions, displaced endometrial cells are eliminated by immune surveillance mechanisms, particularly through the action of macrophages and natural killer cells. Failure of immune clearance allows these cells to implant, survive, and proliferate within the peritoneal environment (5).

Angiogenesis is essential for the survival and growth of ectopic endometrial lesions, with vascular endothelial growth factor (VEGF) playing a central role in neovascularisation. VEGF is produced not only by activated macrophages but also by ectopic endometrial cells themselves, promoting lesion vascularisation and persistence (6) (7). The presence of ectopic endometrial tissue induces a chronic inflammatory response within the pelvic cavity, further facilitating lesion development. Endometriotic lesions, particularly ovarian endometriomas, are strongly hormone-dependent and are sustained by ovarian steroid hormones, especially estrogen (5)

IV. STEMCELLTHEORY

The stem cell theory of endometriosis is a relatively recent concept that extends beyond traditional explanations such as retrograde menstruation. This theory proposes that endometriosis can originate from a small population of stem cells possessing self-renewal and differentiation capabilities (8). Multiple stem cell sources have been implicated in the initiation and progression of endometriosis, including endometrial stem cells, menstrual blood-derived stem cells, and bone marrow-derived stem cells. The primary source is endometrial stem cells (EnSCs), which are predominantly located in the basalis layer of the endometrium and are responsible for the cyclical regeneration of the uterine lining (9). These cells possess strong self-renewal capacity and multilineage differentiation potential, which are essential for normal endometrial repair. In endometriosis, EnSCs are thought to play a crucial role in disease development. During retrograde menstruation, these stem cells may reflux through the fallopian tubes into the peritoneal cavity, where they can adhere to the ovaries, peritoneum, or other ectopic sites. If these cells evade immune clearance and successfully induce angiogenesis, they may implant and give rise to ectopic endometriotic lesions (10) (11).

Another important source is menstrual blood-derived stem cells (MenSCs). These cells, isolated from menstrual blood, exhibit mesenchymal stem cell–like properties, including high proliferative ability and immunomodulatory functions. MenSCs have been implicated in the establishment and maintenance of ectopic endometriotic lesions due to their enhanced survival, migration, and differentiation capacity (12).

A third significant source is bone marrow-derived stem cells (BMDSCs). These stem cells originate from the bone marrow and have been shown to contribute to endometrial regeneration following menstruation (13). Under conditions of inflammatory dysregulation and altered hormonal signalling, BMDSCs may be aberrantly recruited to ectopic sites such as the ovaries, fallopian tubes, or even distant organs, where they can differentiate into endometrial-like cells.

This ectopic differentiation activates immune responses and chronic inflammation, ultimately promoting lesion formation (14). Strong evidence supporting the contribution of bone marrow-derived stem cells to the endometrium comes from studies of female allogeneic bone marrow transplant recipients. In these individuals, donor-derived endometrial cells were identified in endometrial biopsies using human leukocyte antigen (HLA) typing, demonstrating that bone marrow-derived mesenchymal stem cells can differentiate into human uterine endometrial cells (13) (15). Unlike the retrograde menstruation theory, which primarily explains pelvic disease, the stem cell theory provides a compelling explanation for the development of endometriosis at extra-abdominal sites

V. CEOLOMICMETAPLASIATHEORY

Coelomic metaplasia is a well-recognised theory explaining the pathogenesis of endometriosis. The coelomic metaplasia theory postulates that endometriosis originates from the metaplasia of specialised cells that are present in the mesothelial

lining of the visceral and abdominal peritoneum. Hormonal or immunological factors are thought to stimulate the transformation of normal peritoneal tissue or cells into endometrium-like tissue (16). The coelomic metaplasia theory may explain the occurrence of endometriosis in pre-pubertal girls (17). However, the usual driving force of endometrial growth, estrogen, is not present in the pre-pubertal girls, and therefore this condition may be different from endometriosis that is found in women of reproductive age (16 and 17). Ectopic endometrial tissue has also been detected in female fetuses, and it has been suggested that endometriosis may be a result of defective embryogenesis (18).

According to this theory, residual embryonic cells of the Wolffian or Müllerian ducts persist and develop into endometriotic lesions that respond to estrogen (19). Furthermore, recent theories that are put forward suggest coelomic metaplasia to be the origin of the adolescent variant of the severe and progressive form of endometriosis. However, this theory is imperfect because endometriotic lesions are found in areas outside the Müllerian duct. Others have also proposed that endogenous biochemical or immunological factors induce resident undifferentiated cells to differentiate into endometrial-like cells in the ectopic sites, resulting in endometriosis (20). This suggestion is supported by studies describing hormone-dependent transformation of peritoneal cells into Müllerian-type cells (16,20)

VI. IMMUNEDYSREGULATION

Cell-mediated immunity plays a crucial role in the occurrence of endometriosis. The immune system (leukocytes) recognises that the endometrial tissue is not present in its normal position. Some studies show there is decreased cytokine and NK cell activity. This immune modification leads to the prolongation of endometriotic lesions and an unfavourable condition for conception. (21)

Here are some of the immune cells affected by endometriosis: Macrophages in endometriosis Macrophages play an important role in endometriosis. The affected women contain 50% of immune cells in the peritoneal fluid. The neuropeptide pathway handles the classic chemokine receptors like CCR2, promoting macrophage secretion of chemokines and metalloproteinases, like enzymes, which may lead to the formation of lesions. The peritoneal macrophage reduced the phagocytic activity. (22)

NK cells in endometriosis NK cells' activity are reduced by decreased cytotoxicity of CD56 and $CD16^{+}$ in the peritoneal fluid. The cytokines (TGF-beta, IL-6, and IL-15) decrease the NK cell activity. (2) T-cells in endometriosis T-cells, such as Th2 and Th17, increased in the peritoneal fluid. These Th2, Th17, and cytokines elevate the inflammation and endometriosis cell proliferation. The imbalance between Th1 and Th2 leads to the elevation of TNF-alpha, IL-6, and IL-17, which again damage the endometrium. (2)

VII. OXIDATIVE STRESS

Oxidative stress depends on ferroptosis Ferroptosis is an iron-dependent programmed cell death by the accumulation of lipid peroxides; it is a different form of apoptosis, necrosis, and autophagy. (23)

The iron levels are elevated in the peritoneal cavity in endometriotic women when compared to normal women. The increased amount of iron leads to oxidative stress, which favours local disruption of the peritoneal mesothelium and stimulates cell proliferation and generation of reactive oxygen species. (23), (22)

VIII. HORMONAL IMBALANCE

Endometriosis is also known as a steroid-dependent disorder; that's why it mostly affects the reproductive age. The imbalance between estrogen and progesterone may lead to the occurrence of endometriosis. Estrogen and progesterone play an important role in the menstrual cycle phase (24). In healthy endometrium, estrogen and progesterone release some receptors such as ER-alpha and ER-beta and PGR. These receptors are useful in angiogenesis, cell proliferation and neurogenesis when the ratio between alpha and beta is the same. (25) But in the case of endometriosis, the ratio is abnormal; ER-beta is higher than ER-alpha, and ER-alpha induces the action of the PGR receptor and increases the progesterone resistance. The imbalance ratio releases inflammatory mediators, such as cytokine TNF-alpha, leading to inflammation.

IX. ENDOMETRIOSIS ASSOCIATED INFERTILITY

Endometriosis is one of the major causes of infertility. Some of the factors that influence infertility are (26)

Factor 1 As mentioned earlier, the ectopic endometrium that forms in the fallopian tubes causes inflammation in the surrounding tissues. This inflammation can lead to partial blockage of the tubes, preventing the meeting of sperm and egg, thereby reducing the chances of conception. (27) The lesions that develop on the ovaries due to the presence of endometrial foci stimulate the immune system, leading to the release of cytokines and the formation of reactive oxygen species (ROS). (28) These ROS damage the ovarian tissue, reducing both the quantity and quality of oocytes (eggs), which in turn lowers the chances of fertility.

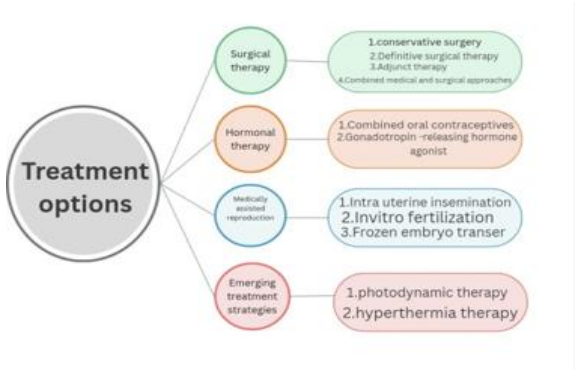
Factor 2 The stem cell can reach any place in the body. When it reaches the ovary, it leads to the formation of lesions on the ovary (endometriomas) that damage healthy ovarian tissue, and this reduces ovarian reserve and interferes with normal ovulation, which impairs fertilisation. (29) Stem cells in ectopic sites release cytokines, prostaglandins, and growth factors, which create a chronic inflammatory state that damages sperm and oocytes and impairs fertilisation and embryo implantation. (30)

Factor 3 Absence of sexual intercourse due to severe pelvic pain (dysmenorrhea). (31)

Factor 4 Oxidative stress can damage the adjacent ovarian cortex and decrease the ovarian reserve (32)

Factor 5 Altered oestrogen and progesterone balance leads to impaired folliculogenesis and oocytes. (33)

Factor 6 dysregulation of the immune system: release of inflammatory mediators such as cytokines, TNF, IL-6, and Th-17 leads to damage to ovarian tissue, which leads to loss of fertility in women (34)



Treatment of endometriosis-associated infertility

X. SURGICAL TREATMENT FOR ENDOMETRIOSIS

Surgical treatment options are the initial step for the treatment of endometriosis.
There are four surgical treatment options presented; they are
1. conservative surgery
2. Definitive surgical therapy
3. Adjunct surgical treatment
4. Combined medical and surgical approaches

1 conservative surgery:
Surgery aims to overcome the endometriosis and also retain the functions of the uterus and ovarian tissue, and secure the pelvic anatomy. In this therapy, the endometriosis lesions are seen, and the lesions are removed. Surgery is done when the lesions are larger than 3 cm in diameter. The removal of lesions in the uterus leads to improvement of fertility outcomes. (35) Laparotomy is a surgical procedure that may be necessary for advanced cases with extensive adhesion or involvement of the uterine arteries, ureter, bladder, and bowel. (36)

2. Definitive surgical therapy: The definitive treatment of endometriosis is a total abdominal hysterectomy. This type of surgery was performed on those women who have the advanced disease and who have completed childbearing. (37)

3. Adjunct surgical treatment: Presacral neurectomy and laparoscopic uterosacral nerve ablation (LUNA) have been performed for intractable endometriosis-associated chronic pelvic pain. (38)

4. combined medical and surgical approaches: The combined treatment for endometriosis to treat advanced endometriosis is a combination of medical and surgical therapies. The therapy is used in preoperative and postoperative conditions. (39) Postoperative therapy is a short medical therapy lasting about 6 months. levonorgestrel releasing intrauterine device (LNG-IUD), which shows a greater result in the reduction of dysmenorrhea

Emerging treatment strategies: n assumption is created that the hormonal suppression-based treatment causes more side effects than the safe and effective treatment of fertility. Some of the non-coding RNAs are introduced in the treatment of infertility-associated endometriosis MicroRNA-based treatments are promising new fertility treatments. Stem cells have regenerative capacity and replace dead tissue and inflammation by decreasing intrauterine adhesion and fibrosis. Stem cells increase endometrial thickness.

XI. MEDICALLY ASSISTED REPRODUCTION (MAR) IN ENDOMETRIOSIS INDUCES INFERTILITY

MAR is a group of treatment options for women who have suffered endometriosis-associated infertility. The techniques shown below
1. Intrauterine insemination (IUI)
2. In vitro fertilization (IVF)
3. Frozen embryo transfer (FET)

1. Intrauterine Insemination
It is one of the first techniques used in the treatment of endometriosis-associated infertility in mild to moderate conditions. The working principle of IUI is to bypass the cervical mucus and deposit and prepare the motile sperm directly injected into the cavity of the uterus at the time of ovulation. This technique improves fertility chances. (31) IUI is coordinated with controlled ovarian stimulation (COS); the success rates are increased. Studies show that women with mild to moderate endometriosis associated with infertility improve with IUI. The advantage of IUI is it's a cost-effective and less invasive option for young women at an early stage. (40)

2. In vitro fertilization:
IVF is most effective in cases of moderate to severe endometriosis-associated infertility, bypassing the barriers that cause endometriosis, including pelvic adhesion, tubal abnormality, and inflamed peritoneal environment. IVF begins with COS using gonadotropins to promote the development of multiple mature follicles. The ova are released and are taken from the vagina through ultrasound guidance. Then ova are fertilized in the laboratory via conventional insemination or intracytoplasmic sperm injection (ICSI). (41) The fusion of ova and sperm forms the embryo, which is cultured for several days and then transferred into the uterus. IVF is indicated for those women with advanced endometriosis. (42) One of the disadvantages of IVF is the expensive and time-consuming process. More than 30-40% of women with endometriosis achieve live birth per IVF cycle. Some of the factors that affected the failure of IVF are age, severity of disease, and decreased ovarian reserve. (43)

3. Frozen embryo transfer:
It is an effective treatment for endometriosis associated with infertility, especially for those who had the treatment of IVF. FET is the process where embryos are crafted in the course of previous IVF cycles, and that embryo is frozen and stored, then placed in the uterus at the time of implantation. This technique helps to preserve the uterine environment. FET improves the probability of pregnancy. One of the advantages of FET is it reduces the risk of ovarian hyperstimulation syndrome (OHSS). Some of the research found that FET is better than the fresh embryo transfer in endometriosis-associated infertility (44). During the procedure of FET, some of the precautions should be taken. FET in combination with HRT by this reduces the risk of recurrence of endometriosis lesions. (29) FET increases the 40% pregnancy rate in endometriosis-associated infertility. The disadvantages of FET are cost and the number of clinic visits. (40)

XII. EMERGING TREATMENT STRATEGIES

Main treatment options for endometriosis use hormonal suppression, such as GnRH analogues or progestins. Although these reduce symptoms, they have many side effects, do not improve fertility, and do not correct the underlying molecular defects; hence, there is a need for non-hormonal targeted therapies Photodynamic and hyperthermia therapy

Endometriosis is a known cause of infertility due to adhesions, inflammation, and distorted anatomy. These treatments that involve the removal of lesions might improve fertility, but do not have a direct effect on fertility improvement (45).

Photodynamic therapy (PDT) is a new and experimental treatment approach being studied for endometriosis. It aims to selectively destroy endometriotic lesions while causing minimal damage to surrounding healthy tissues. Photodynamic therapy uses three components: a photosensitising drug, Light of a specific wavelength and oxygen present in tissues. When these three combine, they produce reactive oxygen species (free radicals) that destroy abnormal cells (46). The process involves a photosensitizer (e.g., porphyrins, 5-aminolevulinic acid) being administered. The drug preferentially accumulates in endometriotic tissue rather than normal tissue (47).

The pelvic area is exposed to light (laser/LED) during laparoscopy. This light activates the photosensitizer, which generates toxic oxygen radicals (46). These oxygen radicals cause endometriotic cells to undergo cell death (apoptosis/necrosis). Blood vessels supplying lesions are also damaged, reducing recurrence. This therapy is being researched as an adjunct or alternative to surgery and hormonal therapy

Hyperthermia therapy involves raising the temperature of tissues to 40–45°C for a specific duration. At this temperature, abnormal cells are more sensitive to heat, cellular proteins denature, blood supply to lesions is impaired, and cells undergo apoptosis or necrosis (48). The process involved is localised heat applied to endometriosis implants. This heat causes protein denaturation in ectopic endometrial cells, leading to microvascular damage and reduced blood supply to lesions (48), which eventually induces cell death (apoptosis). Reducing inflammation and pain signalling also decreases lesion viability and recurrence. This therapy is considered an adjunct to surgery, not a replacement (49).

XIII. STEM CELL THERAPY

Stem cell properties of self-renewal and differentiation make their use attractive to replace potentially damaged tissues and inflammation by reducing intrauterine adhesions and fibrosis, improving endometrial thickness, and promoting endometrial regeneration (50). To date, the use of stem cells for treating endometriosis, and in particular endometriosis-associated infertility, offers an attractive option because of its trophic and immunomodulatory properties (51).

XIV. MEDICAL MANAGEMENT

Hormonal Therapy: Hormonal therapy is the most commonly used medical treatment for women with endometriosis, primarily aimed at suppressing menstruation by inducing a temporary state of pseudo-pregnancy or iatrogenic menopause (52). Although hormonal therapy does not cure endometriosis, it effectively controls pain, delays or avoids surgical intervention, and supports long-term disease management (53). First-line treatment typically includes progestins, while combined oral contraceptives are widely used off-label to manage symptoms (54).

Second-line therapy consists of gonadotropin-releasing hormone agonists (GnRH-a) such as goserelin, leuprolide, nafarelin, buserelin, and triptorelin. These agents initially stimulate LH and FSH secretion, but continuous administration suppresses GnRH receptors, leading to reduced ovarian oestrogen production and regression of endometriotic lesions. GnRH agonists are effective in relieving endometriosis-associated pain and may improve fertility outcomes when administered before assisted reproductive techniques (55).

However, their use is associated with hypoestrogenic adverse effects, including amenorrhea, hot flashes, and bone loss, which can be minimised through add-back therapy using low-dose oestrogen, progestins, or other agents (56). GnRH antagonists such as elagolix, relugolix, and Linzagolix act by directly blocking GnRH receptors, providing rapid therapeutic effects without the initial flare seen with agonists (57). Elagolix, an FDA-approved oral GnRH antagonist, has demonstrated significant reduction in dysmenorrhea, non-menstrual pelvic pain, dyspareunia, analgesic use, and fatigue (46) in women with endometriosis (58). Emerging hormonal therapies, including aromatase inhibitors, selective oestrogen receptor modulators (SERMs), and selective progesterone receptor modulators (SPRMs), are currently under investigation as potential treatment options (5).

Overall, hormonal therapy remains a cornerstone in the management of endometriosis, with treatment

selection individualised based on symptom severity, reproductive goals, and tolerance to side effects (59).

Anti-inflammatory therapy: Anti-inflammatory drugs, mainly nonsteroidal anti-inflammatory drugs (NSAIDs), have a symptomatic role in managing endometriosis-induced infertility by addressing the inflammation that contributes to reproductive dysfunction (60). Endometriosis is associated with chronic pelvic inflammation that negatively affects ovarian function, endometrial receptivity, oocyte quality, sperm function, and embryo implantation (61). These inflammatory processes generate reactive oxygen species (ROS) and cytokines, which cause oxidative stress and tissue damage, impairing fertility (62). However, NSAIDs primarily provide pain relief and do not directly treat infertility mechanisms such as adhesion formation, ovarian cysts, or altered tubal anatomy, which also play significant roles in infertility related to endometriosis (63). While NSAIDs are important in symptom control, their impact on improving fertility outcomes remains limited (63). The inflammatory environment affecting oocyte maturation and sperm function is an area of ongoing research (64). Emerging anti-inflammatory treatments targeting specific cytokines and pathways could offer future fertility benefits by restoring a healthier reproductive microenvironment (64, 65).
However, more clinical evidence is needed to establish anti-inflammatory drugs as a direct treatment for infertility caused by endometriosis (65). In short, NSAIDs and other anti-inflammatory drugs play a supportive role in managing inflammation and pain in endometriosis, but their effect on reversing infertility is indirect and limited (60,63).

XV. CONCLUSION

Endometriosis-associated infertility is a multifactorial disease that includes severe pelvic pain, dysmenorrhea, dyspareunia, dyschezia, hematochezia, and altered pelvic anatomy. Some of the theories explain the pathophysiology of endometriosis, such as retrograde menstruation, stem cell theory, coelomic metaplasia, immune dysregulation, and oxidative stress. There is no single theory that could explain all aspects of endometriosis Treatment options for the treatment of endometriosis-induced infertility are surgical, medical, medically assisted reproduction (IUI, FET), and emerging treatment strategies. All the treatments have been approved recently to improve fertility in women who suffer from endometriosis

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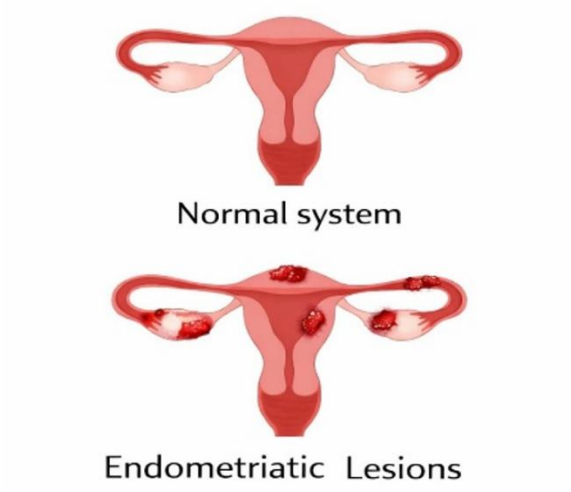

Fig:1 occurrence of lesions in endometriosis

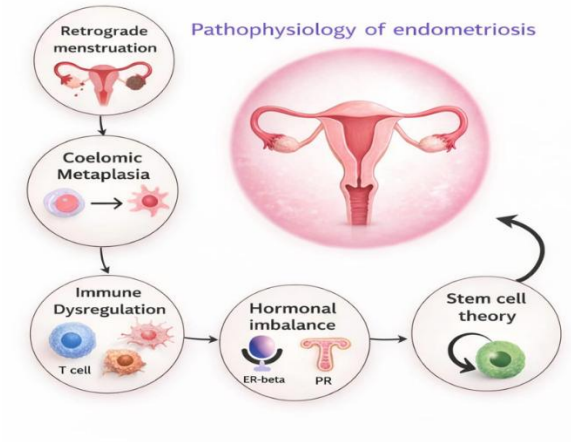

FIG:2 Pathophysiology of endometriosis

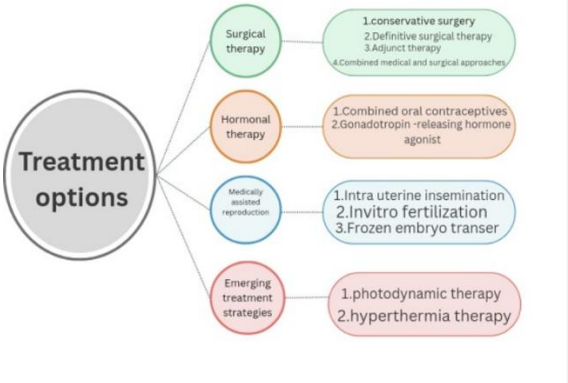

FIG:3 treatment options for endometriosis