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Review Article

Endometriosis-associated Infertility: Treatment Modalities

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Abstract

Endometriosis is a common chronic inflammatory condition, which severely affects women of reproductive age. It is defined as the implantation of endometrial glands and stroma outside the uterine cavity. These ectopic endometriotic lesions may be asymptomatic, but most commonly, women present with pelvic pain, adnexal mass(es), dyspareunia, infertility, dyschezia, dysuria, and rarely dyspnea, thus adversely affecting women's overall health. It not only hampers their quality of life but also has a deleterious effect on their reproductive ability and personal relationship. Endometriosis is a multifactorial disease and is known to affect fertility but does not totally prevent conception. Management of endometriosis lies whether the complaint is about pain or about infertility. Different treatment modalities have been employed to treat endometriosis, starting from conservative to surgical management. This literature review will highlight on how endometriosis affects fertility and the various treatment options available to treat women presenting with endometriosis-associated with infertility.

Key words: Anti-Mullerian hormone, Dysmenorrhea, Dyspareunia, Endometriosis, *In vitro* fertilization, Infertility

INTRODUCTION

Endometriosis is an estrogen dependent gynecological disease with a prevalence of 10-15% that affects women of reproductive age.[1] The true prevalence is difficult to quantify as wide ranges have been reported in the literature. Studies have suggested that about 25–50% of infertile women are found to have endometriosis, and 30–50% of women with endometriosis are infertile.[2]

The prevalence of endometriosis has increased to as high as 25–50% in infertile women[3] which infers that it has a negative effect on woman's child-bearing ability.

Endometriosis is one of the most common gynecological disease presenting to the outpatient gynecology clinic. It is defined as the presence of endometrial glands or endometrial tissues outside the uterine cavity in ectopic locations. The most common site of these endometrial implants are as follows: Ovaries being the most frequently involved, followed by anterior/posterior cul-de-sac, broad ligament, uterosacral ligament, uterus, fallopian tubes, sigmoid colon, and appendix. However, the presence of extra-peritoneal ectopic endometrial tissues has also been reported in the literature such as lungs, diaphragm, upper abdomen, and the central nervous system.[4]

Endometriosis may present as variable clinical presentations, some women are asymptomatic, while others present with painful cyclic menstruation, chronic pelvic discomfort, painful sexual intercourse (dyspareunia), dyschezia, and subfertility, which severely hamper the quality of life in these women. Endometriosis is a histological diagnosis. Laparoscopy and biopsy of the endometriotic implant are considered as the gold standard for the definitive diagnosis of endometriosis.[5]

The treatment in these patients depends upon the presenting complaint, severity of the disease, and the desire to preserve fertility.

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Conservative treatment includes gonadotropin-releasing hormone analogs, oral contraceptive pills, prostaglandins (PG), aromatase inhibitors (AIs), and non-steroidal anti-inflammatory drugs (NSAIDs). Surgical management is indicated for pain alleviation in advanced cases of endometriosis[6] and also for releasing pelvic adhesions that may impact reproductive functionality.

ETIOLOGY OF ENDOMETRIOSIS

The pathogenesis of endometriosis is multifactorial. It is a benign but a progress and an aggressive disease. There are several theories hypothesized explaining the pathogenesis of endometriosis, but no single theory explains all the disease manifestations. One of the most popular and accepted theory proposed by Sampson is the theory of retrograde menstruation. In his theory, he hypothesized that the backward flow of endometrial cells shed during causes pelvic endometriosis.[7] The transfer of these progenitor cells from the uterine endometrium to ectopic location results in implantation of these tissues into the peritoneum, ovaries, fallopian tube, and cul de sac, which then grows in the presence of cyclic hormones resulting in a chronic inflammatory reaction resulting in pain, pelvic adhesions, and infertility issues.[8,9]

Another theory by Halban, 1925, proposed that the spread of endometrial cells to extra-peritoneal and distant extra-pelvic sites could be through the lymphatic channels and the vascular system. Hematogenous spread of the endometrial cells is best explained by this theory in cases of endometriosis of the lungs, forearm, and thighs.

Another contrasting theory by Meyer *et al.*, 1924 hypothesizes that endometriosis arises from the metaplasia of the coelomic epithelium. Majority of the female reproductive tract is derived from the Mullerian duct and the Mullerian duct is a derivative of coelomic epithelium.

This theory postulates that the coelomic epithelium is multipotent and has the ability to differentiate into different histological cell types. Endometriosis has also been reported to have found in prepubertal girls, women with an absent uterus and also in men, rarely.[10] These examples support this theory of coelomic metaplasia.

It is recently speculated that the survival of endometrial cells outside the uterine cavity is due to the overexpression of CD 147 which is an anti-apoptotic factor.[11] Due to the imbalance of pro and anti-apoptotic factors, endometrial cells stay in these ectopic locations.

Recent studies have also speculated that endometriosis could be due to bone marrow-derived stem cells.[12] A recent study identified the presence of chimerism in the endometrial cells of four women who underwent bone marrow transplants, thus suggesting that bone marrow-derived stem cells contributed to the overgrowth of the endometrium in these patients.[13]

Moreover, in contrast, molecules such as the fibroblast growth factor receptor have been over-expressed in ectopic locations causing these females to suffer from endometriosis. Studies have also demonstrated that in patients with post-surgery recurrence, there was overexpression of fibroblast growth factor receptor 1.[14]

Among the various endometriotic lesions, peritoneal lesions induce an inflammatory reaction which enables the activation of T helper cells. When the acute phase resolves, the process of chronic inflammation is carried by monocytes and macrophages, resulting in peritoneal adhesion and formation of new blood vessels (angiogenesis).

Endometriosis is an estrogen-dependent disease. During the luteal phase of a woman with a normal menstrual cycle, progesterone is secreted and in response to the progesterone, endometrium results in the transformation from proliferative to secretory phase. In a patient with endometriosis, a reduced response to progesterone is seen and hence estrogen aggravates the pathological process of inflammation and growth of the endometrial cells, thus causing the symptoms of endometriosis.[15]

CLINICAL MANIFESTATIONS

The most commonly presenting debilitating symptom in patients with endometriosis is pain. These women have typical symptoms of dysmenorrhea (painful menstruation), often starting with menarche. They also complain of dysuria (painful urination), dyspareunia (painful sexual intercourse), dyschezia (pain on defecation), chronic pelvic pain, and fatigue.[16] Studies show that endometriosis is strongly associated with infertility. As an estimation, 30–35% people with endometriosis are associated with infertility and vice versa.[17]

The mechanism explaining the link between endometriosis and infertility is poorly understood. It is believed that the endometrial implants cause major pelvic adhesions, thus impairing oocyte release from the ovary or inhibiting ovum transport due to tubal adhesions, thus negatively impacting fertility by decreasing fecundity in women with endometriosis.[17]

The initial evaluation for endometriosis in a patient is made by complete detailed history taking and physical examination, including the bimanual pelvic examination.

History and physical examination mostly yield a significant number of findings which are suggestive of endometriosis. On bimanual examination, dyspareunia, a fixed retroverted uterus, uterosacral ligament nodularity, deep infiltrating thick lesions appearing as nodules, and adnexal masses can easily be identified by palpation.

Tumor marker, like, CA-125 is usually raised in women with endometriosis; however, it should not be taken into consideration as they lack sensitivity and specificity.[18] Biomarkers obtained from the serum, plasma, and urine is of no clinical significance in these patients.[19] Ultrasound of the pelvis can help in identifying ovarian endometrioma but is a poor imaging modality in identifying peritoneal and extrapelvic implants. Upon comparison between transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) pelvis in detecting deep rectosigmoidal and retrocervical endometriotic lesions, TVUS had a sensitivity of 98%, specificity of 100%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 98%, and accuracy of 99%. Whereas, MRI had sensitivity of 83%, specificity of 98%, PPV of 98%, NPV of 85%, and accuracy of 90%.[20] Transvaginal sonography (TVS) not only helps in detecting endometriotic lesions but also aids in reflecting adhesion and help in visualizing pelvic fluid on sonography. Several reviews have concluded that TVS can reliably detect endometriotic lesions in comparison to MRI.[20]

In cases of moderate to severe endometriosis, where the symptoms have not resolved in spite of undergoing medical management, laparoscopy is indicated.[21]

Laparoscopy is the gold standard in diagnosing and inspecting endometriotic lesions.

The definitive diagnosis should be made after confirming the positive laparoscopic findings with histopathology of the lesions to exclude any other cause.[22] However, laparoscopy should only be reserved only for the symptomatic patient who presents with pain secondary to adhesions or for treating stage III OR IV endometriosis.

TREATMENTS

Depending upon the age, severity, location, and desire for future fertility, treatment must be tailored for each patient, whether medical or surgical management is needed.

Medical Management of Endometriosis

NSAIDS

Ibuprofen, indomethacin, naproxen, suprofen, mefenamic acid, lexofenac, and diclofenac are some of the examples of NSAID's. They are used as the first line in treatment for pain alleviation in patients who present with dysmenorrhea. Their mechanism of action is by inhibiting cyclooxygenase, an enzyme that converts arachidonic acid into PG, prostacyclin, and thromboxanes. The thromboxanes play a major role in platelet adhesions. PG causes vasodilation and increases the temperature in the hypothalamus, thus causing pain.

NSAIDs inhibit this conversion and prevent the production of PG and thromboxanes. They are successfully used in treating patients with dysmenorrhea, menorrhagia, and pain associated with intrauterine devices (IUDs). They ameliorate menstrual pain by decreasing the level of PG F2 alpha in the endometrial cells. It also acts by decreasing the intrauterine pressure and menstrual blood loss. In a study comparing the effect of pain relief in a patient using NSAIDs versus acetaminophen, relief by NSAIDs was 80–85% and it was superior in achieving symptomatic relief in a patient with dysmenorrhea as compared to acetaminophen.[22]

Combined oral contraceptive pills (COCP)

The use of hormonal therapy for a period of minimum 6 months has shown to suppress and regulate ovarian hormonal imbalance. It has also aid in alleviating pain associated with endometriosis.[23] Studies have shown that there is a significant decrease in the size of endometriomas with the use of OCPs. This is mostly due to an increment in apoptotic rate in the endometrium which is ectopic and also there is downregulation of cell proliferation.[24] Continuous administration of COCPs has been proven to be more effective in ameliorating the symptoms of painful menstruation, reducing the size of endometriomas and pelvic pain in comparison to cyclic administration.[25] Studies have shown that the long-term use of cyclic OCPs for 3 years following surgical resection of endometriosis resulted in a decrease of recurrence rate of endometriosis by 50%.[26] Review by Vercellini *et al.* suggested that ovulation suppression is an important reason in preventing the recurrence of endometriomas. In addition to prescribing the drugs to the patient, potential side effect should also be kept in mind. The side effect of oral contraceptives includes bloating, weight gain, mood swings, increase in breakthrough bleeding, and increase in blood clot formation. There is also a decrease in libido. Hypoestrogenic state causes menopausal symptoms such as night sweats, hot flushes, vaginal dryness, and fatigue.

Progestins

Progestins are synthetic compounds that mimic the action of progesterone, they come in various concentrations, doses, and forms of administration such as oral administration, injectables, intrauterine administration, and subdermal implantation. The oral route drugs include

medroxyprogesterone acetate given 30–60 mg/day, dienogest (visanne) 2 mg/day, cyproterone acetate 10–12.5 mg/day, and norethisterone acetate (primolut N) 2.5–5 mg/day. Injectable, depot medroxyprogesterone acetate (Depo Provera) can be given in a dose of 50 mg/week intramuscularly. Subdermal implants (Implanon) are a single rod of 68 mg inserted subdermally in an outpatient setting using it is applicator by a trained nurse or a physician. This is effective for 3 years and must be replaced/removed after 3 years or whenever women desire fertility. IUD such as levonorgestrel intrauterine system (Mirena) contains 52 mg of levonorgestrel which can be placed into the uterus, also in an outpatient setting by a physician or a trained nurse. This can be used up to 5 years, but a follow-up transabdominal ultrasound every 12 months is recommended to check for its position if the women are unable to feel the thread.

Progestin works by ovulation suppression. It negatively inhibits the pulsatile effect of gonadotrophin-releasing hormone (GnRH) which further works by decreasing the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary hence resulting in ovarian suppression with a low level of ovarian steroids.[27] This long-standing hypoestrogenic state results in the transformation of ectopic endometrium which leads to atrophy, decidualization, and alteration in steroid receptor binding ligand in the endometrium.

Since endometrial foci consist of a very few progesterone receptors such as PR-β, which is undetectable, and PR-α, which is reduced. As a result, progestin causes downregulation in further synthesis of these receptors and acts by working on progesterone receptor expression and progesterone resistance. Progestin also alleviates the pain by suppressing the production of interleukin-8 (IL-8), tumor necrotic factor-α (TNF-α) induced nuclear factor-χ-β. It increases the production of nitric oxide. It also has a negative effect on angiogenesis which is (formation of new blood vessels) on the ectopic endometrium by suppressing the transcription of basic fibroblast growth factor, vascular endothelial growth factor, and cysteine-rich angiogenic inducer [CYR61]).[28] The side effect of progestin includes abnormal uterine bleeding, nausea, breast tenderness, fluid retention, and depression.

Androgen

The use of androgen creates a hyper-androgenic state by inhibiting FSH and the LH, which results in the atrophy of the endometriotic implants, thus useful in the treatment of dysmenorrhea. Danazol is an androgenic drug, one of its major reported side-effects includes hirsutism (excessive hair growth). Weight gain, vaginal spotting, voice change, acne, and muscle cramps are some of the other reversible adverse effects seen with this drug. With the hypoestrogenic effect of danazol, premenopausal symptoms such as hot flushes, amenorrhea, and vasomotor symptoms are noticed, but these are reversible with the cessation of the drug use. The recommended dose of danazol is 400 mg/day; the dosage can be increased till there is a cessation of menses.[29]

GnRH agonist

The GnRH agonists are among the most effective medications available to treat endometriosis. The side effects of GnRH agonists include menopausal-like symptoms such as vaginal dryness, hot flashes, and osteopenia.

They are believed to work by making an estrogen-deficient state starting immediately after 2 weeks of beginning the therapy. They work by increasing the release of GnRHs by triggering the pituitary to release FSH and LH, which result in a flare effect and negatively inhibits GnRH, that is, FSH and LH by downregulating them, resulting in a hypoestrogenic state.

Gelety *et al.* confirmed that the symptoms of the flare effect were exacerbated more in the follicular phase. Hence, it is advised to give GnRH agonist in the mid-luteal phase.[30] Furthermore, Meldrum *et al.* concluded that there was a rapid progressive pituitary suppression when GnRH is given in the beginning of mid-luteal phase.[31]

GnRH agonists are generally used to shrink the size of the endometrial implants; it is also used before surgeries to decrease the size of these implants and endometriomas; also, it helps to prevent the removal of excessive scar tissues.

Due to the hypoestrogenic state, women experience menopausal symptoms. The side effects of GnRH agonists include vaginal dryness, hot flashes, and osteopenia. Hence, the use of GnRH is limited to 12 months only. It is also recommended that add-back therapy be initiated after 6 months of GnRH agonist use if it was not started previously. Usually, progestins, the combination of progestins and estrogen, have been used for add-back therapy.[32] Loss of bone mineral density is reversible with the cessation of the GnRH agonists.

AIs

Aromatase inhibitors (AIs) works by supressing estrogen production in the ovarian and peripheral tissue. There are three generations of AIs, the first, the second (fadrozole and formestane), and the third generation (anastrozole and letrozole). The route of administration for the first and second is intramuscular injection. Third generation AI's can be administered orally. Amongst the three generations of Ais, the most potent is the third generation.

They increase the level of FSH in premenopausal women, thus mimicking a menopausal state. Adverse effect of it includes symptoms similar to postmenopausal state. Aromatase activity has been found in ectopic endometrial lesions as compared to the normal endometrium, ectopic endometrium lesions have estrogen sources, which converts them to PGE2 leading to additional growth of ectopic endometrial tissue. Therefore, AIs work by inhibiting this vicious cycle.[33] A study by Patwardhan *et al.* confirmed that AIs have a pain-controlling effect. It decreases the size of endometrial implants and improves the quality of life when combined with OCPs or GnRH-agonists.[34]

Surgical Treatment for Endometriosis

Surgery is indicated when medical treatment has failed. Severity of symptoms and the presence of large endometriomas may direct to provide surgical intervention sooner.

Laparoscopy or laparotomy is the choice in the management of patients with deep pelvic endometriosis, more specifically in patients with advanced-stage endometriosis. It includes removal of endometriotic lesion by excision, coagulation, ablation, interruption of nerve to alleviate pain, and restoration of the anatomy. Surgical option remains debatable in the early stage of the disease; however, it has shown to improve the symptoms and progression of the disease. In patients with ovarian endometrioma having a cyst >3 cm, technique of ablation and coagulation revealed lower chances of recurrence with dysmenorrhea and dyspareunia and the rate of cyst recurrence was diminished too.[35] Studies have shown that the recurrence of endometrial implants after endometrial ablation versus those women who did not undergo endometrial ablation was almost zero.

Moreover, after the ablation treatment, patients did not exhibit retrograde menstruation or ectopic endometriotic implants. This method not only helped in ameliorating the pain but also stood as an alternative to hysterectomy in women who wish to preserve future fertility.[36]

DISCUSSION

Endometriosis and Infertility

Despite several researches and studies, the exact correlation between endometriosis and infertility is unknown and this topic is very debatable. Several ideologies have been proposed to explain the relationship between the two, which includes abnormalities in endocrine and ovarian function, altered hormonal function of endometrium, impaired luteal phase defect or multiple LH surges, progesterone resistance, deleterious effect on spermatozoa, dysfunctional utero-tubal ability, anti-endometrial antibodies, pelvic adhesion, and fallopian tube inflammation due to peritubular adhesions, which can impede the patency of the tube and thus result in impaired oocyte pickup from the ovaries and diminished ovum transfer along the tube. Impaired folliculogenesis is also seen in this patient with endometriosis.[37]

In patients with ovarian endometriosis, cystectomy of endometriomas may result in a greater loss of ovarian reserve because the surgery involves the removal of a larger amount of ovarian stromal tissue to which these endometriotic lesions are adhered, this result in damage and decreased ovarian reserve.[38]

In women with chronic endometriosis, a decreased ovarian response is seen due to increased concentration of IL-1b, IL-8, IL-10, and TNF.

Elevated amount of cytokines, specifically IL-6 in the peritoneal fluid of these women, is also known to cause inhibition of sperm motility.[38,39] Embryo implantation is also affected by complex behavior of ectopic endometrial implants.

Due to these functional disorders of the endometrium, abnormal uterine contractions are seen in these patients.

For fertilization to occur, there has to be an optimal uterine cavity that enables sperm transportation to undergo capacitation in the ampulla of the fallopian tube to fertilize the ovum. Uterine contractility is very important for shedding the endometrium every month, for conception, maintenance of ongoing pregnancy, and gamete transfer. When uterine contractions are abnormal, symptoms of painful menstruation, endometriosis, and infertility are seen. Retrograde menstruation and the presence of endometriotic lesions are seen in the abdomen when the uterine contractibility is abnormal.[40] Another etiology seen in these patients is the dysfunction of hypothalamic-pituitary-ovarian axis which can lead to infertility due to the lengthened follicular phase and diminished peaked LH concentration, also known as luteal phase defect.

Pituitary dysfunction causes downregulation of the endometrial receptivity, poor oocyte quality, and thus disrupted synthesis of follicles.[37]

Treatment for Endometriosis-related Infertility

Evidence-based treatment for infertility associated with endometriosis includes the combination of medical and surgical treatment, after ruling out the other causes of infertility such as male factor, thyroid dysfunctions, hyperprolactinemia, and premature ovarian insufficiency.

In patients with endometriosis, staging is important to determine the treatment of infertility in such patients.

Endometriosis is staged from the stage (I-minimal, II-mild, III-moderate, and IV-severe) based upon the exact location, extent, and depth of the endometriotic implants, presence of the scar tissues, and presence of endometrial tissues in the ovaries.[41]

The *in vivo* intrauterine insemination with or without follicle stimulation is used in patients who have mild to moderate endometriosis. It involves the transfer of sperms high in the fundus of the uterine cavity. The sperm can be of partner or donor sperm, this treatment is mainly used for patients having mild endometriosis with patent tubes.

In vitro fertilization and embryo transfer (IVF-ET) is the treatment of choice in women who have compromised tubal function due to adhesions secondary to endometriosis, male factor infertility, and previous IVF treatment failures.

IVF is an *in vitro* process that involves the transfer of one or more embryos in the uterine cavity by externally fusing it in the laboratory.

For males, who have severely low-quality sperm with abnormal morphology, intracytoplasmic sperm injection is done. IVF ET is being encouraged for women having advanced endometriosis and it is considered as the first line of therapy.[40]

IVF-ET has produced a pregnancy rate of 56.1% in comparison to significant lower pregnancy of 37.4% with surgery alone.[42] However, the surgical procedure has been effective in removing the entire visible lesion during the laparoscopic intervention. Laparoscopic adhesiolysis has shown to improvise the fertility rate in patients with more severe stages of endometriosis.[36]

Future Perspective for Endometriosis-related Infertility

Future treatment is more targeted toward the molecular level, including use of immunotherapies to genes and tissue factors which are seen in endometriotic lesions. Low levels of Anti-Mullerian Hormone (AMH) are also seen in women who complain of infertility. It is used as a tool to access ovarian reserve.[43] It is notably reduced in women who have had ovarian surgeries. Therefore, women who desire fertility, AMH level can help in selecting in prioritizing and choosing patients for ovarian cystectomy as a fertility treatment.[44]

CONCLUSION

Endometriosis is a debilitating disease. Early diagnosis and management can halt the progression of this inflammatory disease and on the contrary, late diagnosis can lead to a decrease in reproductive ability and infertility.

Endometriosis impairs fertility in a multifactorial way, which adversely affects the ovarian reserve and child-bearing capacity depending on the stage and severity of the disease.

Early diagnosis and treatment are the key to this progressively and worsening disease. IVF is the best treatment of choice in patients who wish to conceive but have severe endometriosis which has impeded their normal child-bearing ability.

Medical treatment can only ameliorate the symptoms but shows no effect in increasing pregnancy rate. Treatment, therefore, must be individualized and taken into consideration as per the desire of the patient.

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AUTHORS' CONTRIBUTIONS

Jaanam Khan – Data collection, reviewing, and preparing the manuscript. Mutarba Khan, Arbaab Khan – editing the manuscript and reference management.

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