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## Endometriosis: An overview of disease and treatment

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### Abstract

Endometriosis is defined as the presence of endometrial like tissue outside the uterus, which induces a chronic inflammatory reaction, scar tissue and adhesions that may distort a woman's pelvic anatomy. The estimated prevalence of endometriosis in the general population is as high as 10% and is increased in females with infertility. The gold standard of diagnosis is surgical visual inspection of the pelvic organs through laparoscopy. Serum cancer antigen-125 levels may be increased in women with endometriosis but it is a poor diagnostic tool in comparison to laparoscopy. The principal aim of the therapy is to relieve symptoms, resolution of existing endometrial implants, and prevention of new foci of endometrial tissue. Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, and dyspareunia. Articles were selected based on their currency and relevance to the discussion.

**Keywords:** Endometriosis, infertility, laparoscopy, menstruation, estrogen

### Introduction

Endometriosis, a gynecologic pathology, is defined by the presence of a tissue similar to uterine endometrium, which is located in places other than uterus (ovaries, fallopian tubules, tissue lining the pelvis) [1]. This is distinct from adenomyosis, in which endometrial tissue is confined to the uterine musculature. Size of endometrial tissue ranges from microscopic endometriotic implants to large cysts (endometriomas) [2]. The presentation and evaluation of the disease is variable but in some cases, disease can persist as a mild or can also disappear. Other cases show severe symptomatology because of invasion and tissue infiltration, chocolate cysts formation, pelvic blockage that can affect other organs [1].

### Types

1. Superficial endometriosis
2. Deep infiltrating endometriosis
3. Ovarian endometriosis(cysts)

### Superficial endometriosis

It is painful type of endometriosis and very less tissue involved, it cannot be detected by sonogram and can only be detected by laparoscopy. Tissue size 1- 2 cm [2, 3].

### Deep infiltrating endometriosis

It is very rare type of endometriosis and most painful. Here deep lesions are seen that penetrate bowel, bladder, even the vagina and the penetration of the tissue is about 5 mm and even more [2, 3].

### Ovarian endometriosis

Here the chocolate cysts are seen and the chocolate colour is due to brown, bloody fluid that fills the cyst and finally looks like soft chocolate. The cyst is about 3-4 cm in diameter and may extend upto 15 cm (rare). Infertility is the common complication associated with this type of endometriosis [2, 3].

### Epidemiology

Endometriosis is a very common debilitating disease that occurs in 6 to 10% of the general female population. Prevalence of endometriosis women with pain, infertility or both is about 35 to 50%. Typically endometriosis presents in young women with a mean age of 25- 29 years and mostly uncommon among adolescents. About 25 to 50% of infertile women have endometriosis and 30 to 50% of women with endometriosis are infertile [4].

**Table 1:** Prevalence of endometriosis in different countries [4]

Countries	Prevalence
USA	16.2%
France	11.7%
Italy	14.4%
UK	15.3%
Canada	14.7%
Brazil	24.0%
Korea	9.3%

**Prevalence of endometriosis in India: (based on Kolkata survey, endometriosis society, INDIA)**

At least 26 million women between the ages of 18 and 35 were afflicted by endometriosis. 5% girls below 18 who complained of dysmenorrhea are affected by endometriosis and between the ages of 21 to 25 years the incidence of endometriosis was 18%, 21 to 30 years which is the optimum age for reproduction the incidence was 55%.

**Causes [5]**

The factors that initiating or causing endometriosis are unknown. Some of the causes are

- a. Familial history (common in identical twins)
- b. Retrograde menstruation
- c. Metaplasia

**Risk factors**

Having short menstrual cycle and heavy bleeding during periods lasting longer than 6 days. Early puberty is also one of main risk factor and others include alcohol abuse, cervical / vaginal outlet obstruction [5].

**Signs and symptoms**

Usually 20 to 25% of patients are asymptomatic but common symptoms include Dyspareunia, dysmenorrhea, chronic pelvic pain and infertility, [2, 4] painful bowel movements, catamenial diarrhea, rectal bleeding, hematuria and dysuria [6, 7].

**Diagnosis [3]**

Based on diagnosis, endometriosis is divided into 4 stages

**Stage 1:** Lesions are minimal and isolated.

**Stage 2:** Lesions are mild and multiple, adhesions are also seen.

**Stage 3:** Lesions are moderate, deep, and superficial, with clear adhesions.

**Stage 4:** Lesions are multiple, severe, both superficial and deep with prominent adhesion.

**Table 2:** Association of endometriosis women age with stages [8]

Endometriosis women age group (in years)	Stage 1	Stage 2	Stage 3	Stage 4
20-25	8%	7%	12%	7%
26-30	15%	16%	24%	16%
31-35	9%	12%	32%	8%
36-40	3%	8%	12%	4%

**Diagnostic Tests**

1. Physical examination: It includes speculum and bimanual examination. In speculum examination, the health

professional inserts an instrument called a speculum into the woman's vagina and speculum helps to spread apart the walls of the vagina, allowing the health professional to see the cervix and the walls of the vagina [2].

2. Bimanual pelvic examination often follows the speculum examination and it is done to check a woman's pelvic organs (such as the uterus and ovaries). The speculum is removed and the health professional inserts two gloved, lubricated fingers into the woman's vagina while pressing on her abdomen with the other hand (bimanual means with two hands). This allows the health professional to feel where and how large the woman's pelvic organs are [2].
3. Laparoscopy: It is considered as gold standard for diagnosing endometriosis. Surgeon makes a tiny incision near navel and inserts a slender viewing instrument called as laparoscope to detect endometrial tissue outside the uterus. In some cases biopsy is done to obtain information about the location, extent and size of endometrial implants to determine the best treatment options [2].
4. Transvaginal ultrasound: It helps in diagnosing endometriomas, bladder lesions
5. Deep Ultrasound: It is readily available and inexpensive tool for diagnosing endometriosis nodules [3].
6. Trans rectal ultrasound: It is used to demonstrate rectal involvement in endometriosis, depth of infiltration by endometriosis and to detect lesions on the posterior bladder wall [2, 7].
7. MRI: It is used in diagnosing recto sigmoid lesions and bladder endometriosis. Typically the lesions that can be detected with MRI are the compounds that contain blood products [7].
  - Hemorrhagic “power burn”: Lesions appear bright on T1 fat saturated sequences
  - Small solid deep lesions: May be hyper intense on T1 and hypo intense on T2.

**Pathophysiology**

The pathogenesis of endometriosis remains unclear and is subject to much debate; potential mechanisms include:

**Retrograde menstruation**

During retrograde menstruation blood flows backward into the fallopian tube instead of leaving the body through the vagina. It occurs due to the asynchronous uterine contractions and is normally seen in 90% of women but only 10% prevalence of the disease is seen when large volume of menstrual blood reaches the pelvic region (9). These displaced menstrual blood contains endometrial cells that stick to the pelvic walls and surfaces of pelvic organs where they grow and leads to development of endometriotic implants. These implants establish local vascularity and continuous to thicken and bleed over the course of each menstrual cycle [10, 11].

**Role of cell mediated immunity**

Women with endometriosis demonstrate functional changes in cells of the immune system including monocytes / macrophages, NK cells, cytotoxic T-lymphocyte and B cells. Decreased surveillance, recognition, destruction of misplaced endometrial cells causing possible facilitation of their implantation and development of endometriosis. Peripheral blood monocytes (PBM) and peritoneal macrophage (PM)

play key role. In normal fertile women with no endometriosis, PBM and PM Suppress endometriosis cell proliferation (invitro). In endometriosis women, PBM stimulate and PM inhibit endometrial cell proliferation. The cytotoxic effect of PM is inversely correlated to endometriosis but here the stimulatory action of the PBM is dominant and leads to endometriosis [12].

#### **Transforming growth factor beta activity increased in peritoneal fluid**

It is detected using mvlv cell growth inhibition assay. The concentration of TGF-beta is increased in peritoneal fluid of women and leads to development of endometriosis, compared to both fertile without endometriosis and infertile without endometriosis individuals [13].

#### **8.4 Bisphenol-A and phthalates**

Bisphenol-A, phthalates have particular concern as passing reproductive and developmental toxicants. Bisphenol-A (BPA) has widespread exposure for human populations and poses important public health challenges because it is a high production volume phenolic chemical used in the manufacture of polycarbonate plastics and epoxy resin coatings in canned food containers. BPA has the ability to interact with estrogen receptors and stimulate estrogen production and also alter gonadotropin hormone secretion that leads to increase in endometrial cell proliferation and finally causes endometriosis. Like BPA, phthalates are also high production volume chemicals and are metabolized quickly and excreted in urine without evidence of accumulation within the body. Phthalates shows antiandrogenic effect by reducing testosterone production and at high doses reduces the estrogen production [14].

#### **9. Goals of the treatment**

- Halt the growth and activity of endometriosis lesion
- Treat the symptoms ( pain, dyspareunia)
- Prevent there recurrence

#### **10. Medical treatment for endometriosis**

##### **10.1 First line treatment**

The choice should be based on patient preferences, side effects, efficacy, cost and availability. For oral contraceptives, further benefits such as contraceptive protection, long term safety, and control of menstrual cycle should be considered. Progestins used are medroxyprogesterone acetate, norethindrone acetate, dienogest, etonogestrel implant and IUD – levonorgestrel [15].

##### **10.2 Second line treatment**

Due to side effects, they should only be prescribed to women for whom other treatments have proven ineffective. Drugs included are NSAIDS, GnRH analogues, Danazol, gestrinone [15].

##### **10.3 Emerging treatments**

More clinical studies are needed, especially to assess their long term efficacy and side effects. Drugs include Aromatase inhibitors, GnRH antagonists, Selective Progesterone Receptor Modulators (SPRMs), Selective estrogen Receptor Modulators (SERMs) [15].

#### **NSAIDS**

Clinicians consider analgesics or NSAIDS to reduce

endometriosis associated pain, after discussing about adverse effects commonly associated with use of these medications [15]. COX2 expression has recently been demonstrated in ectopic endometrial cells in concentration higher than eutopic endometrium. The release of prostaglandins in ectopic endometrial cells seems to be involved in pathogenesis of endometriosis and high concentration of prostaglandins were found in the peritoneal fluid of affected women. So inhibiting the progesterone release by blocking COX pathway, endometriosis associated pain and growth of ectopic cells is inhibited. ROFECOXIB: 25 mg OD for 6 months [15].

#### **Progestins**

Reducing pain to 70% - 100% using medroxyprogesterone acetate and norethindrone acetate pain has reduced to 70% - 100% [16]. Norethisterone acetate allows good control of uterine bleeding, chronic pelvic pain and shows positive effect on calcium metabolism and no effects on lipoprotein metabolism at low dosages. Dose: 2.5mg/day for 12months provided pain relief and amelioration of gastrointestinal symptoms are observed. Medroxy progesterone acetate at a dose of 100 mg/day is more effective in controlling pain but it is burdened by several side effects. Levonorgestrel releasing intrauterine device (IUD-LNG) was more effective treatment in reducing symptoms of dysmenorrhea. A uniform suppression of the endometrium in progesterone IUD users is always found after six months of treatment, whereas the insertion of IUDs releasing 20-30 micrograms levonorgestrel induce a profound uniform suppression of the functional endometrium throughout the uterus only after four weeks [15].

#### **Danazol**

Danazol acts by inhibiting the midcycle FSH and LH surges and preventing steroidogenesis in corpus leuteum and is as effective as any of the newer agents, but with higher incidence of adverse effects (acne, facial hirsutism, vaginal dryness, breast atrophy, weight gain). DOSE: 600-800mg/day BID (infertile/severe), 200 mg-400 mg (mild) BID and therapy is inhibited during menstruation. Duration of the treatment is about 6 months to 9 months [16].

#### **Dienogest**

Dienogest shows a high selectivity for the progesterone receptors and powerful progestinic effect on endometrium, also causes minimal changes in serum lipid profile and carbohydrate metabolism. These are synthetic oral progestin with strong progestational and moderate antigonadotrophic effects, with no androgenic, glucocorticoid, mineralocorticoid effect. Dienogest has fewer hypoestrogenic adverse effect [17]. Dienogest 2 mg/day for 52 weeks [15].

#### **Gestrinone**

Acts by inhibiting the pituitary gland and consequently the release of gonadotrophins. The resulting ovarian suppression determines atrophy of both endometrium and endometriosis lesions [15]. It is effective therapy for treating painful symptoms associated with endometriosis but shows severe androgenic effects. Dose: 2.5mg twice a week [18].

#### **GnRH antagonists**

GnRH antagonists bind to receptors in the pituitary but have a longer half-life than normal GnRH and there by result in down regulation of the pituitary axis and hypoestrogenism [18]. To reduce negative side effects of estrogen deprivation and

allow longer treatment periods, ADD BACK therapy with norethindrone acetate or combination of estrogen and progesterone has been advocated [16]. Elagolix 150 – 200 mg/day up to 24months.

### **Aromatase inhibitors**

These are effective for the treatment of endometriosis and pelvic pain in premenopausal and postmenopausal women [18]. Aromatase inhibitors can be used along with oral contraceptives pills, progesterone, GnRH agonists, because they reduce endometriosis associated pain [17]. An over expression of aromatase enzyme, the main responsible factor for estrogen synthesis in ectopic endometrium, has been demonstrated in endometrial tissue. Aromatase catalyzes the conversion of the steroidal precursors into estrogens, which stimulate the expression of the enzyme COX2. The estrogens produced in the endometrial tissue through aromatase promote the growth and invasion of endometrial lesion and favour the onset of pain and prostaglandin mediated inflammation. Aromatase inhibitor on contrary, lead to a reduction of extra ovarian estrogen concentration. Anastrozole 1-5mg/day, LETROZOLE 2.5mg/day. Duration of therapy is about 3-5 years [17].

### **Selective estrogen receptor modulators**

These interact with estrogen receptors as agonists or antagonists depending on the target tissue. In patients with endometriosis, the rationale for their use is related to the estrogen – agonistic activity on bone and plasma lipoproteins and estrogen antagonistic effect at endometrial level [15]. TAMOXIFEN 10- 20 mg/day. Duration of therapy is about 3-5years.

### **Selective progesterone receptor modulators**

SPRMs represent a class of progesterone receptor ligands that display progesterone agonist, antagonist or mixed agonist-antagonist activity on several progesterone target tissues. SPRMs inhibit ovulation, but estradiol levels remain in physiological range. Mefepristone -50 mg for 6 months OD was effective in improving the symptoms and causing regression of endometriosis without significant side effects [15].

### **Surgical treatment**

Aim of the Surgery is to remove macroscopic endometriosis implants and restore normal pelvic anatomy. However surgery may not be able to completely restore pelvic anatomy or to stop inflammatory process. Hence it is important to weigh benefits versus risk. Laparoscopy is preferred to laparotomy because of advantages of minimal tissue damage, faster recovery, and shorter hospital stay [19].

### **Recurrence after surgery**

Endometriosis has propensity to recur with time after conservative surgery. If recurrence occurs, initial treatment should be appropriate analgesics and oral progestogens, IUD-LNG, gonadotropin agonists are found to reduce the frequency and severity of recurrent endometriosis-related symptoms [20].

### **Treatment for endometriosis and infertility**

In the management of infertility associated with endometriosis, clinical decisions are difficult because few randomized controlled trails are conducted to evaluate and

compare the effectiveness of the various forms of treatment. The clinical management of an infertile couple should take age of the female, duration of infertility, male factor, duration of medical attention, pelvic pain, stage of endometriosis, and family history in to account. Effective, evidence based treatments of endometriosis associated infertility include conservative surgical therapy and assisted reproductive technologies. Patients with endometriosis who are interested in fertility may gain limited benefits with medical surgery. Although theoretically advantageous, there is no evidence that the combination of medical and surgical treatments can significantly enhance fertility and it may unnecessarily delay further fertility therapy. The two treatment options, in this case include surgery or invitro fertilization and embryo transfer (IVF – ET) [6].

### **Role of pharmacist**

Pharmacist need to have a regular discussion with patient to ensure any progression of the symptoms. Changes in the pain experienced, altered symptoms from the involvement of other organs, changes in the regularity/irregularity of the menstrual cycle should be cause for further discussion [21].

### **Life style modification**

Pharmacists are committed to assist and support the patients to make lifestyle changes that improve the patients' health and wellbeing and also have an essential role in health promotion through the disease management by providing support and much needed information to the patient, in addition this will facilitate quality of care to improve quality of life, reduce pain and prevent further progression of disease. Since there is no cure, medical treatment, life style modifications must be effective and safe to use until the age of menopause or until pregnancy is desired. Dietary fat influences production of prostaglandins, chemicals that stimulate uterine contractions and effect ovarian functioning. Foods rich in omega3fattyacids, N-acetylcysteine and vitamin D, in addition to the increased consumption of fruits, vegetables and whole grains exert a protective effect in reducing the risk of development and possible regression of disease. Physical activities like cycling, aerobics are the another aspect of lifestyle modification as it seems to have protective effect against disease that involve inflammatory process since it induces an increase in the systemic levels of cytokines with anti-inflammatory and antioxidant properties and also acts by reducing estrogen levels [22].

### **Conclusion**

The studies have demonstrated that, endometriosis is a common chronic disease in women and can also affect fertility in many ways at different levels and the Pelvic pain, infertility in the presence of endometriosis necessitate individualization of therapy to achieve treatment goals. Recurrence rates of pain and endometriotic nodules will be final judge in determining the most suitable therapy. The only way to make a firm diagnosis direct visualization of the disease by endoscopy or laparotomy. Timely intervention and appropriate, multifunctional treatments may restore quality of life, preserve or improve fertility and lead to long term effective management in the absence of permanent cure.

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