

Endometriosis: An Update

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Definition and Prevalence

Endometriosis is the presence of endometrial-like tissue outside the uterus in women of reproductive age from all ethnic & social groups. This endometrial tissue may be found in the ovaries, peritoneum, uterosacral ligaments and Douglas pouch. Ectopic endometrium in the uterine muscles is known as adenomyosis. Extra-pelvic endometrial tissues; e.g. on diaphragm, umbilicus are rarely found.

Endometriosis is present in 10% of the general population. It reaches 21% in infertile women and 82% in women with chronic pelvic pain.



Predisposing Factors

- 1-Hyperestrogenism. e.g. in cases of fibroids, metropathia, estrogen producing tumors.
- 2-Cervical stenosis
- 3-Curettage



Theories of etiology

- 1-The retrograde reflux of menstrual tissue from the fallopian tubes during menstruation.
- 2-The celomic metaplasia theory. Mesothelium covering the ovaries invaginates into the ovaries, then undergoes metaplasia into endometrial tissue.
- 3-The embryonic rests theory. The müllerian remnants in the recto-vaginal region differentiate into endometrial tissue.

The risk of endometriosis is directly proportional to the duration of exposure to menstruation. i.e., early menarche, shorter cycle length, longer duration of flow, or reduced parity. The risk decreases for personal habits that may relate to decreased estrogen levels i.e., smoking, exercise.



Endometriosis and Irradiation

In the 1970s, a group of Rhesus monkeys was exposed to various types of irradiation with very high doses. The risk of developing endometriosis significantly increased in the irradiated animals. Therefore; it is assumed that women receiving whole-body or abdominal exposure to high doses of X-rays should be considered to be at higher risk of developing endometriosis than the unexposed. The explanation for this effect may be through interference with normal immune system function.



Gross-Macroscopic-Picture

1-Adenomyosis: characterized by:

- The uterus is symmetrically or asymmetrically enlarged, firm with hyperplastic endometrium.
- Presence of multiple dark spots on uterine serosa
- Cystic spaces filled with altered blood throughout the uterine wall
- Whorled appearance with no capsule (D.D. fibroid)

2-Ovarian endometriosis: both ovaries are usually enlarged. The typical lesion is chocolate cyst 5-6 Cm filled with altered blood. There is thickening of tunica albuginea and ovaries are surrounded by adhesions.



Gross-Macroscopic-Picture

3-Pelvic endometriosis: This is characterized by multiple colored nodules seen on the uterosacral ligaments and filling the Douglas pouch. They are often surrounded by adhesions leading to fixed retroversion of the uterus.



Microscopic Picture

1-The finding of ectopic endometrial glands and stroma is the corner stone to establish a diagnosis of endometriosis. It is present in 50-70% of cases.

2-Most histopathologists consider fibrosis, chronic inflammation, and/or hemosiderin-laden macrophage highly suggestive of endometriosis.



Diagnosis

I-Symptoms: A large percentage of women affected with endometriosis are asymptomatic. Pelvic pain and infertility are the commonest presentation.

1-Dysmenorrhoea, deep dyspareunia, dyschezia or dysuria

2-Chronic pelvic pain

3-Ovulation pain

4-Cyclical or perimenstrual symptoms (e.g. bowel or bladder) associated with or without abnormal bleeding. E.g. cyclic haematuria or bleeding per rectum

5-Infertility/subfertility (due to adhesions preventing ovum release or pickup, diminished ovarian reserve with low oocyte and embryo quality).

6-Chronic fatigue



Diagnosis (Cont.)

II-Signs: Pelvic examination reveals:

1-Pelvic tenderness

2-Fixed retroverted uterus

3-Tender utero-sacral ligaments. This sign has the highest positive likelihood ratio.

4-Enlarged ovaries on examination is suggestive of endometriosis.

The diagnosis is more certain if deeply infiltrating nodules are found on the utero-sacral ligaments or in the pouch of Douglas and/or visible lesions are seen in the vagina or on the cervix.



Diagnosis (Cont.)

Investigations:

1-Trans-vaginal ultrasound has no value in diagnosing peritoneal endometriosis but can be useful both to make and to exclude the diagnosis of an ovarian endometrioma. It may have a role in the diagnosis of disease involving the bladder or rectum. Trans Rectal Sonography may be useful for diagnosing rectovaginal endometriosis.

2-CA 125 is useful as a marker for disease monitoring and follow-up but not for diagnosis.



Diagnosis (Cont.)

3-Laparoscopy: “gold standard test”. It can be done at any time during the menstrual cycle but better avoided within 3 months of hormonal treatment to avoid under-diagnosis. Identification of endometriotic lesions depends on the surgeon’s experience. They are usually nodular but may take the form of peritoneal windows. Deeply infiltrating endometriosis may show as minimal disease, resulting in underestimation of disease severity.



Diagnosis (Cont.)

4-Histopathology: of any biopsy is needed to confirm diagnosis. Removal of an ovarian cyst for histological confirmation is recommended if the cyst is > 3 Cms diameter. Histologic confirmation requires the presence of 2 of the following:

1-hemosiderin-laden macrophages

2-endometrial epithelium

3- glands

4- stroma

Ovarian endometriosis as a single finding occurs in $< 1\%$ of endometriosis patients, the rest having mostly pelvic &/or intestinal endometriosis as well.



Diagnosis (Cont.)

Differential Diagnosis

Causes of any of the following:

1-Causes of dysmenorrhea

2-Causes of dyspareunia

3-Causes of Generalized pelvic pain. Endometritis, ovarian torsion, pelvic adhesions or PID

4-Infertility. Anovulation, luteal phase defect, tubal adhesions or cervical factor of infertility.

5-Irritable bowel syndrome



Staging of Endometriosis

Several staging systems were proposed to stage endometriosis from minimal up to severe disease, the most often used is the revised AFS (stage I to stage IV). It assesses the location and depth of the disease together with type and extent of adhesions and assigns each parameter a score. The following scores are indicative for the corresponding stage:

- A score of 1-5: Stage I (minimal disease)
- A score of 6-15: Stage II (mild disease)
- A score of 16-40: Stage III (moderate disease)
- A score > 40: stage IV (severe disease):



Staging of Endometriosis

Martin in 2006 proposed a grading system to address the level of certainty of the laparoscopic diagnosis of endometriosis. The laparoscopic Grades of Certainty consists of 4 Grades:

A-Grade 1: Possible endometriosis - Peritoneal vesicles, red polyps, yellow polyps, hypervascularity, scar, adhesions.

B-Grade 2: Suggestive of endometriosis. Chocolate cyst with free flow of chocolate fluid.



Staging of Endometriosis

C-Grade 3: Consistent with endometriosis - Dark scarred (puckered pigmented or mixed color) lesions, red lesion on fibrous scarred background, chocolate cyst with mottled red and dark areas on white background.

D-Grade 4: Endometriosis. Dark, scarred (or puckered, pigmented) lesions at first surgery.




Treatment (Cont.)

I-Control of pain:

1-NSAIDs: act by 2 mechanisms: 1) Central inhibition of PG synthesis; 2) Activation of endogenous opioids & serotonergic mechanisms.

2-Suppression of ovarian function for 6 months. All drugs are equally effective. This can be achieved using:

a-Progestagens (First choice): exert an antiproliferative effect by causing initial decidualisation of endometrium followed by atrophy. Medroxyprogesterone acetate is effective at a dose of 30-100 mg/day depending on clinical response. It can be given at a dose of 150 mg IM every 1-3 months.



Treatment (Cont.)

b-Combined oral contraceptives: Any low-dose combined oral pill containing 30-35 mg of EE2 used continuously induce pseudopregnancy and achieve amenorrhea can be used. Pills can be given either continuous or cyclic. Symptomatic relief is reported in 60-95% of patients after continuous use. Estrogens in oral contraceptives potentially may stimulate the proliferation of endometriosis. However, the reduced menstrual bleeding that often occurs in women taking oral contraceptives may be beneficial to women with prolonged frequent menstrual bleeding, which is a known risk factor for endometriosis.

c-The levonorgestrel IUD (Mirena).



Treatment (Cont.)

D-GnRH agonist treatment with 'add-back': Treatment for up to 2 years with combined E and P 'add-back' appears effective and safe in terms of pain relief & bone density protection. Progestagen only is not protective. Careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density. Examples include leuprorelin, buserelin, nafarelin, and goserelin. They are inactive orally and must be administered IM, Sc or intranasally. Side effects of GnRH are due to the associated hypo-estrogenism. The most important is decreased bone loss. Where treatment is restricted to 6 months the effect on bone mineral density virtually resolves by 12 months.



Treatment (Cont.)

Add-back can be achieved by tibolone 2.5 mg/day, or by an E/P combination in the form of conjugated oestrogens 0.625 mg combined with medroxyprogesterone acetate 2.5 mg or with norethindrone acetate 5 mg), estradiol 2 mg and norethisterone acetate 1 mg. However, some concern remains about the long term effects of GnRH analogues on bone loss. In a recent report, bone mineral density reduction occurred during long-term GnRH agonist use and was not fully recovered up to 6 years after treatment.



Treatment (Cont.)

E-Gestrinone: is a 19-nortestosterone derivative with androgenic, anti-P, anti-E, and anti-Gn properties. It creates a hormonal environment that results in the cellular inactivation & degeneration, not disappearance, of endometriotic implants. Amenorrhea occurs in 50-100% of women. The standard dose is 2.5 mg twice a week.

F-Danazol: It acts by several mechanisms to achieve amenorrhea and prevents the development of future endometriotic lesions:

- 1- suppresses gonadotropin secretion
- 2- inhibits steroidogenesis
- 3- increases metabolic clearance of oestradiol and progesterone
- 4- interacts with endometrial androgen and progesterone receptors

Treatment (Cont.)

Danazol produces a high-androgen, low-estrogen environment not favorable to support growth or future seeding of endometriosis. The dose is 400 mg/day which is increased gradually to achieve amenorrhea & relieve symptoms. Side effects are related to the androgenic & hypo-estrogenic effects of the drug such as weight gain, fluid retention, acne, hirsutism, hot flushes, atrophic vaginitis, reduced breast size, reduced libido, fatigue, emotional instability and deepening of voice is irreversible.

Danazol is contraindicated in patients with liver disease, hypertension, congestive heart failure, impaired renal function and pregnancy.



Treatment (Cont.)

G-Aromatase inhibitors: Currently, there is lack of data to support their use in the management of endometriosis. It is likely that aromatase inhibitors be a part of a combination therapy with other ovarian suppressant drugs.

H-Anti-angiogenic therapies, progesterone anatagonists: They are suggested as potential treatment for endometriosis. However, limited data is available to advocate wider use.



Treatment (Cont.)

II-Laparoscopic treatment is the treatment of choice. Laparotomy is reserved for patients with advanced disease in whom laparoscopic surgery is not possible. It may take the form of excision, fulguration or adhesiolysis.

- Ablation of endometriotic lesions plus laparoscopic uterine nerve ablation (LUNA) in minimal-moderate disease reduces endometriosis associated pain at 6 months. LUNA by itself has no effect. Pre-sacral neurectomy may have a role in women with severe dysmenorrhoea.
- Endometriosis associated pain can be reduced by removing the entire lesions in severe deeply infiltrating disease up to hysterectomy & BSO.



Thank You

