

Endometriosis - A Review

Anuradha Singh, Swati Agrawal*

Department of Obstetrics & gynaecology, Lady hardinge Medical College & Smt SSK Hospital, New Delhi, India

*Corresponding author: Dr. Swati Agrawal, Department of Obstetrics and gynaecology, Lady hardinge Medical College and Smt SSK Hospital, New Delhi, India, E-mail: drswatimail@gmail.com

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Abstract

Endometriosis is a major cause of disability and significantly compromised quality of life in women and adolescents. It is characterized by the implantation of ectopic endometrial glands outside the uterus. The most common sites of implantation are dependant areas of the pelvis, pelvic peritoneum, anterior and posterior cul de sac and uterosacral ligaments, rectovaginal septum, and ureter. Other rare sites include bladder, pericardium, surgical scars and pleura.

Keywords: Endometriosis; Hormone; Urinary bladder; ligaments

Introduction

Endometriosis is estimated to affect 10% of the reproductive age group women. The prevalence ranges from 2-11% in asymptomatic women, 5 to 50% among infertile women, and 5 to 21% among women with severe chronic pelvic pain. In symptomatic women, the prevalence ranges from 49% in patients with chronic pelvic pain to 75% for those whose pain is unresponsive to treatment (1). Endometriosis may be classified as superficial or deep. Peritoneal infiltration <5 mm is defined as superficial endometrioses. The presence of endometrial tissue, fibrosis and hyperplasia with >5mm peritoneal infiltration is defined as Deep Infiltrating Endometrioses (DIE). DIE accounts for 15- 30% of all cases of endometrioses (2).

Literature Review

Pathogenesis and pathophysiology

The development of endometrioses involves interacting endocrine, immunologic, proinflammatory, and proangiogenic processes. Among various theories of the genesis of endometrioses, Sampson theory of retrograde menstrual flow is the most accepted theory which suggests that endometriosis originates from implantation of sloughed endometrial tissue, which is refluxed into the pelvis via fallopian tube during menstruation. The other postulated pathogenesis includes coelomic metaplasia of peritoneal lining into glandular

endometrium and vascular or lymphatic metastasis which leads to the development of extrapelvic lesions (3).

Risk Factors and clinical presentation

Available evidence suggests that women with history of Diethylstilbestrol(DES) exposure, low birth weight and early age at menarche are associated with a greater risk of developing the disease. Other risk factor includes short menstrual cycles, low bone mineral density, low waist-hip ratio and low parity (1).

Women with endometriosis are more likely to have coexistent conditions such as clear cell and endometrioid ovarian carcinoma as well as uterine fibroids, adenomyosis; migraine; interstitial cystitis; Inflammatory Bowel Disease (IBS); ulcerative colitis; various mental health disorders such as depression and anxiety; immunologic disorders like Systemic Lupus Erythromatosus; Rheumatoid Arthritis; Multiple sclerosis; asthma. Cancers like Non-Hodgkin's lymphoma, thyroid and melanoma are also found with increased frequency in women with endometriosis (1).

There are the varied clinical presentation of endometriosis and the severity of symptoms and recurrence usually does not correlate with the staging of diseases. Patients with endometriosis may be asymptomatic and women with stage 1 revised ASRM staging with limited number of lesions and few adhesions may have severe pain, infertility or both in contrast patients with stage 4 endometriosis that may remain asymptomatic

Infertility is associated with endometriosis in almost thirteen to thirty-three percent of the cases. Women with endometriosis may present with chronic pelvic pain, abnormal uterine bleeding, dysmenorrhoea, dyspareunia, dysuria, or defecatory pain. Dysmenorrhea caused by endometriosis typically precedes periods by 24 to 48 hours and is usually less responsive to analgesics like nonsteroidal anti-inflammatory drugs (NSAIDs) and combined hormonal pills due to deep infiltrative lesions.

Pelvic pain due to endometriosis is said to be inflammatory as well as neuropathic in nature with sensitization of the central nervous. Pain may be unresponsive to medical treatment in as high as 30% of cases with endometriosis and may persist even after excision of endometriotic lesions in some women (4).

Examination may be normal in a patient of endometriosis or may reveal abdominal masses on abdominopelvic examination. Per speculum examination may be normal or may reveal red powder burnt lesions on the cervix and posterior fornix which

are tender and bleed to touch. On per vaginum examination, uterus may be retroverted with scarring felt on the uterosacral ligament. Nodularity and tenderness in the pouch of Douglas often suggest active disease. Enlarged cystic masses may be felt in the adnexa because of ovarian endometrioma.

The various laboratory tests which should be done to exclude other causes of pelvic pain include hemogram, urine routine microscopy, and urine culture to rule out infection.

Role of Imaging

Transvaginal ultrasound (TVS) is considered a mainstay for evaluating symptoms associated with endometriosis because of low cost and efficacy. It is useful to determine the number, size, and location (unilateral or bilateral) of the cysts, presence of endometriotic nodules, extent of Pouch of Douglas obliteration, presence of hydronephrosis and presence of hydrosalpinx. The international deep endometriosis analysis groups has elaborated on the steps which have to be followed at the time of the TVS examination. These include routine evaluation of uterus and adnexa, evaluation of mobility of ovaries, and assessment of deeply invasive endometriosis in anterior and posterior pouch (5). Sonovaginography and transrectal ultrasound (USG) are especially useful in diagnosing local rectovaginal endometriosis. It involves vaginal instillation of saline to delineate these lesions.

High-resolution contrast-enhanced Magnetic Resonance Imaging (MRI) has been increasingly used as a non-invasive method to stage the disease before laparoscopy. It is especially suited to visualize superficial implants, adhesions, rectovaginal septum infiltration, depth of rectum and bladder wall infiltration as well as ovarian diseases infiltration. It has been made a mandatory investigation in recent times (6).

Computed Tomography (CT) Scan is used as an alternative to MRI in places where MRI is not available but is said to be inferior to MRI for evaluation of endometriosis.

Tests for Ovarian Reserve

The detrimental impact of endometriosis on ovarian reserve especially in severe cases is well known. These patients have reduced ovarian reserve as well as a steeper decline of ovarian reserve over time. So ovarian reserve tests like Antral follicle count(AFC) and serum Antimullerian hormone(AMH) are indicated before planning medical treatment or surgery for infertility associated with endometriosis. Serum AMH has become popular in recent years and is widely used due to its advantage that it can be performed at any time of the menstrual cycle and its levels are not affected by hormonal medication (7).

Diagnostic laparoscopy is considered as a gold standard for diagnosing endometriosis. It helps in accurate diagnosis and staging of the disease. Laparoscopic findings are variable and may include discrete nodules, endometriotic lesions such as endometrioma, variable colors red white or black lesions (due to hemosiderin deposition): smooth blebs; holes or defects within the peritoneum and flat stellate lesions surrounding scar tissue. Histopathological evaluation of tissue biopsy taken during

the procedure helps to know the extent of endometriosis. It also provides an opportunity to see and treat lesions in the initial stages of the disease.

Role of biomarkers

As endometriosis in early stages may not be detected by imaging, extensive research has been undertaken in the past to search for a biomarker which can serve as a noninvasive diagnostic marker for endometriosis. The most studied biomarker is CA 125. A raised serum CA 125 may be consistent with having endometriosis. It has a positive correlation with disease severity and can be used for postoperative follow up as levels rise usually with recurrence. Sensitivity and specificity for detecting stage 1 to 2 endometriosis is 50% and 72% respectively whereas for stage 3 and 4 endometriosis, it is 60% and 80% respectively (8).

However, it is a nonspecific marker and may be raised in a nonspecific conditions such as liver disease, pelvic inflammatory disease, menstruation, fibroids and ovarian neoplasms. Biomarkers like plasma protein 14, interleukin 6, tumor necrosis PGP 9.5 neural fiber marker, CYP 19 factor; glycoproteins like follistatin, glycodelin A; inflammatory cytokines like interleukin1,6,8, Tumour Necrosis Factor, interferon gamma, CD 40; oxidative stress markers like proteins paraoxonase, HDL, plasma superoxide dismutase ; blood biomarkers like Vascular Endothelial Growth Factor, hormones, autoantibodies, circulating cell-free DNA, T and B cells ; urine biomarkers and endometrial biomarkers have all been studied as noninvasive tests for diagnosis of endometriosis. However, currently there is insufficient evidence to support the routine use of any of these markers to diagnose endometriosis.

Management

Treatment depends on the specific symptoms, the severity of symptoms, the location of endometriosis lesions the goals for the treatment, and the desire for future fertility (9). Medical management of endometriosis is the mainstay of treatment. Progesterone in various groups have proven efficacy. In infertility patients, fertility-preserving treatment without ovulation suppression is usually required and in severe symptoms associated with infertility surgery may be the mainstay of treatment. The various drugs used for medical management include non steroidal anti-inflammatory drugs, combined oral contraceptives, progestins, anti progesterone, gestrinone, gonadotropin releasing hormone agonists, GnRH antagonist and selective progesterone receptor modulators. All available hormonal therapy is suppressive but not curative, so the recurrence of symptoms is common after discontinuation of treatment.

Among first-line therapy combined estrogen-progesterone agents given orally, as a transdermal patch or vaginal rings and progestins(given orally, as depot preparation, implants or levonorgestrel intrauterine system are beneficial for the majority of patients with good relief of pain and symptoms, minimal adverse effect, long term safety as well as low cost. Abnormal vaginal bleeding or breakthrough bleeding is commonly

experienced adverse effect seen with prolonged use of COC or with progestones, especially long-acting progestins, depot medroxy progesterone acetate and LNG IUS. With oral progestins, the breakthrough bleeding can be reduced by modification of doses or schedule. The compliance with progestins can be further improved by counseling patients about this adverse effect of bleeding at the beginning of therapy.

GnRH agonists are indicated when first-line therapy is either contraindicated or ineffective in resolving symptoms or not tolerated. Long term use of GnRH agonists is limited by incidence of hypoestrogenic side effects such as vaginal dryness, hot flashes, and bone mineral density loss. Treatment with GnRH agonists of longer than 6 months duration is combined with add-back therapy with COC or Oral progestins to overcome these adverse effects of hypoestrogenism. In the last few years, GnRH antagonists have been widely studied and are considered better in comparison to GnRH agonists as they maintain sufficient estrogen levels in the body to avoid the vasomotor symptom and loss of BMD. However, these agents are still not recommended for clinical use and require more randomized controlled trials to support their increased effectiveness over other commonly used agents for the treatment of endometriosis and their appropriate dosing schedule (10).

Gestrinone is an anti-progestational and anti-estrogenic agent which creates progesterone withdrawal effect and decreases the number of estrogen and progesterone receptors. It is given in a dose of 2.5 mg to 10 mg weekly with divided doses given daily or three times weekly. It is androgenic but not associated with bone loss.

Aromatase inhibitors like Anastrozole has been shown to have a role in severe and refractory cases of pain due to rectovaginal endometriosis. When combined with OC pills, they have been shown to improve endometriosis associated pain while supporting follicular development and preserving bone mineral density (11). However, it is not approved by the US food and Drug Association for this indication.

Newer nonhormonal therapeutic approaches that have been evaluated clinically with significant efficacy in endometriosis related pain and subfertility are rofecoxib, etanercept, resveratrol, everolimus, cabergoline, and simvastatin. Other drugs with similar pharmacological properties like parecoxib, celecoxib, endostatin, rapamycin, quinagolide, and atorvastatin have been studied on animal models only. Clinical evidence about most agents is still insufficient for their use as replacement therapy in endometriosis. Few drugs like pentoxifylline have shown strong potential for real clinical application (12). Surgery is not indicated for asymptomatic endometriosis or for an incidental finding of endometriosis at the time of surgery. Operative laparoscopy (excision/ablation) is indicated in patients with failed medical management of pain associated with endometriosis. It involves the destruction or removal of endometriotic tissue and adhesions and is effective for the treatment of pelvic pain associated with all stages of endometriosis. Surgical treatment improves spontaneous pregnancy rates in women without other known factors causing infertility but its beneficial role in women undergoing in-vitro fertilization is unclear.

Hysterectomy with removal of the ovaries and all visible endometriosis lesions is indicated in women who have completed their family and have failed conservative or medical treatments. However, women should be informed that hysterectomy will not necessarily cure the symptoms or the disease. About 60% of elevated cardiovascular risk in women with endometriosis is attributed to surgical menopause in these patients.

Excision of ovarian endometrioma may greatly affect the ovarian reserve and benefits of surgery should be weighed against their negative effect in women with future fertility concerns. The need for second surgery should be considered carefully if the woman has had previous ovarian surgery. LUNA has not been shown to be beneficial as an adjunctive treatment to conservative surgery for endometriosis. It offers no additional benefit over surgery alone. However, Presacral neurectomy may be effective as an additional procedure to conservative surgery, to reduce endometriosis-associated midline pain, but it requires skilled surgeon and is a potentially hazardous procedure (9). Endometriomas (≥ 3 cm) need surgical treatment and cystectomy is preferred over drainage and coagulation as it is associated with a lower recurrence of the endometrioma and associated pain (13).

Surgery for deep invasive endometriosis

Surgery is said to improve pain and quality of life in women with deep endometriosis. However, there is an increased risk of intraoperative and postoperative complications which need to be kept in mind. Hormonal contraceptives like LNG IUS, COCs and progestins are recommended for the secondary prevention of endometrioma after surgery for endometriosis in women not planning conception for at least 2 yrs for the secondary prevention of endometriosis-associated dysmenorrhea and treatment of pain associated with extragenital endometriosis disease (9).

Management in endometriosis associated infertility

The management of endometriosis-related infertility is surrounded by controversies and has been a topic of debate. In infertile women, medical therapy either alone or in combination with surgical therapy has not been found to be of any benefit. On the other hand, surgical treatment of endometriosis can jeopardize the ovarian reserve consequent to ovarian injury during the resection of the endometriotic tissue. In cases of mild- to moderate-stage endometriosis, intrauterine insemination with ovarian stimulation after surgical treatment has been shown to improve the reproductive outcome. In cases of severe endometriosis, the treatment needs to be individualized and an option of surgery versus assisted reproduction methods such as *in vitro* fertilization should be discussed with the woman.

Conclusion

Endometriosis remains a challenge to diagnose and manage for the clinicians despite all the advances in the field. More research is needed to develop diagnostic and therapeutic

approaches which can aid in effective treatment and potential cure.

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