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Endometriosis: Current Trends in Management

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Abstract

Endometriosis is most common cause of chronic pelvic pain in women. It affects women both physically and psychologically. Important clinical symptoms of endometriosis include dysmenorrhea, dyspareunia and subfertility. Till date there is no definitive cure for it. Treatment of it is based to relieve its clinical symptoms and to reduce the disease load. Medical management is broadly anti-inflammatory and estrogen suppression therapy. Surgery is gold standard for diagnosis and treatment. Its treatment and loss in work productive days is economic burden for society. A multidisciplinary research is needed for timely diagnosis and appropriate treatment of such disease.

Keywords: Endometriosis; Chronic pelvic pain; Dysmenorrhoea; USG

Introduction

Endometriosis is defined as presence of endometrial glands and stroma outside the uterine cavity, first described by Rokitansky in 1860 [1]. It affects about 7% to 12% of women in reproductive age group. The incidence is high in patients suffering from infertility about 25% to 35% [1]. It is also high in patients with chronic pelvic pain (30% to 55%). There are varied symptoms of the disease. The classical triad for endometriosis is dysmenorrhoea, dyspareunia and sub-fertility [1]. Other symptoms are heavy menstrual bleeding, dysuria, dyschezia, abdominal pain, chronic pelvic pain. It may involve bladder, rectum, and gastrointestinal tract leading to hematuria, hematochezia and constipation.

The most common site of involvement is ovary, utero-sacral ligaments, and pouch of Douglas, pelvic peritoneum, tubes, recto-vaginal septum, and posterior surface of uterus. The rare sites of involvement are pulmonary, sub-diaphragmatic area, paracolic gutters, and scar site of episiotomy, hysterotomy, and cesarean section.

There are various theories for etiology of endometriosis [2]:

1. Sampson's theory of retrograde menstruation
2. Coelomic metaplasia theory
3. Stem cell theory
4. Lymphatic and vascular spread theory
5. Genetic theory
6. Immunological theory
7. Hormonal and inflammation theory

Diagnosis

Diagnosis is mainly by strong clinical suspicion based on symptoms as there is typical history of progressive dysmenorrhoea where the pain increases in duration, severity gradually becoming chronic pelvic pain [2]. Physical examination has poor sensitivity, specificity, and predictive value in the diagnosis of endometriosis [3]. Clinical examination may reveal tenderness in fornices, adnexal mass in presence of chocolate cyst, restricted mobility of uterus and thickening of recto-vaginal septum, nodularity in the posterior vaginal fornix, and visible vaginal endometriotic lesions. Imaging modalities include ultrasound, in which mainly transvaginal scan is helpful. Transrectal USG also is useful when transvaginal cannot be performed and to detect recto-vaginal endometriosis. USG will detect ovarian endometrioma, hematosalpinx, where it will show the homogenous ground-glass appearance of the endometrioma [3]. Hydronephrosis secondary to ureteric endometriosis may be detected by transabdominal USG. Minimal and mild endometriosis is difficult to be diagnosed on ultrasound. MRI is said to be better for diagnosis of moderate to severe and deep endometriosis.

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It should not be ordered as primary investigation for diagnosis of endometriosis.

Role of serum bio-marker CA-125 is controversial. It may be high (>35 mIU/ml) suggesting the presence of endometriosis, its rupture but normal value of CA-125 does not exclude endometriosis [4].

Management

Laparoscopy is the gold standard in diagnosis and management of endometriosis [5]. It is both diagnostic and therapeutic. Visual inspection of endometriotic spots on laparoscopy is also not confirmatory. It has to be proven histologically by presence of glands and stroma both but negative biopsy does not rule out endometriosis. The endometriotic patches may appear as red, pink, bluish-purple, velvety lesions or white powder burnt patches [6]. One should be aware of different appearances of endometriotic spots so as to identify them all and properly treat them in the same sitting of surgery. DIE (Deep Infiltrating Endometriosis) may be missed even at laparoscopy and if diagnosed, it requires expertise to remove it [7].

When endometriosis is diagnosed, the gynecologist should document a detailed description of the appearance and site of endometriosis. The staging should be done as per ASRM/ESHRE or revised AFS classification given in 1997 [1]. Recent classification is ENZIAN which takes into consideration DIE and Endometriosis Fertility Index (EFI).

Endometriosis causes infertility due to immunological, ovulatory dysfunction, alteration in endometrial receptivity and tubal factors in severe cases. Endometriosis causes ovulatory infertility by altering folliculogenesis and ovulation due to inflammation associated with endometriosis. Endometriosis causes immunological infertility due to increased production of ROS by macrophages and poly morphonuclear cells associated with endometriosis which causes increased oxidative stress. Decreased expression of integrins and increased production of cytokines are noted. Endometriosis causes decreased sperm quality and function due to inflammatory toxic effects of the peritoneal fluid and activated macrophages upon the sperms. Endometriosis affects endometrial receptivity by causing progesterone resistance, dysregulation of progesterone receptors and by increased Estrogen production secondary to elevated aromatase enzymes.

Endometriosis is a chronic, recurrent, progressive disorder which affects the quality of life rather than decreasing the survival [7]. Management options are both medical and surgical. It is based mainly on symptoms, patient's age and desire for fertility. Medical management is mainly for patients suffering from pain, dysmenorrhoea, and dysuria. It is also used for prevention and treatment of recurrence and if patient refuses surgery. But if the patient has main complain of infertility, then one has to go for surgical management.

Medical management

There are many groups of drugs being used for medical management of endometriosis. These are described below:

a) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): The pain pathogenesis is through prostaglandin pathway so COX 1 and COX 2 inhibitors are first line therapy in endometriosis associated pelvic pain and dysmenorrhoea. Mefenamic acid and ibuprofen are most commonly used and they are effective in almost 50% to 60% cases when given thrice daily [6].

b) Combined oral contraceptive pills: These are mainly used in women who are not trying for conception. They suppress endogenous release of gonadotropins, reduce menstrual flow and progesterone component decidualized endometriotic implants. They can be used as continuous or cyclic regimen. Continuous regimen for 6 months is more effective in controlling pain and dysmenorrhoea in about 40% to 50% [5].

c) Progestins: They cause atrophy of the endometriotic implants and pseudo-pregnancy state. It can be given for 3 to 6 months continuously and leads to 60% reduction in pain. Various preparations are used such as medroxyprogesterone acetate in 20 mg to 80 mg daily dose, norethisterone 10 mg to 20 mg daily, Injection Depot medroxyprogesterone acetate 150 mg every 3 months for 6 to 9 months, dienogest 2 mg daily for 6 to 9 months [5,6]. Dienogest is fourth generation synthetic progesterone which has recently been proposed as treatment of choice for this condition. Long term progesterone delivery system in the form of LNG-IUS (Levonorgestrel Intrauterine System) is also beneficial in these patients as amenorrhoea is achieved in 88%-92% of patients after 9 to 12 months. It delivers 20 mcg of progesterone daily for five years. It has less systemic side effects and more effective in causing local atrophy of endometrium.

d) GnRH agonists: They cause pituitary desensitization and thereby leading to inhibition of ovarian steroidogenesis. They lead to pseudomenopause and also called medical oophorectomy. Common preparations available are leuprolide acetate 3.75 mg, triptorelin 3.75 mg, goserelin 3.6 mg [4-6]. They are given as monthly injections for 6 months. If one has to give it for longer duration than 6 months then add-back therapy is used to prevent hypoestrogenic side effects and decrease in bone mineral density.

Add-back therapy includes conjugated equine estrogen (0.3 mg to 0.625 mg) combined with norethisterone acetate (2.5 mg to 5 mg) [3].

e) GnRH antagonist: Cetrorelix in dose of 0.25 mg daily or weekly dose of 3 mg for 3 months can also be used [7].

f) Aromatase inhibitors: These agents lead to hypoestrogenism which is responsible for suppression of endometriotic implants. Anastrozole (2 mg) or letrozole (2.5 mg) is use for 6 months continuously [6].

g) Selective Progesterone Receptor Modulator (SPRM): They bind to progesterone receptors and exert varying effects on different tissues. Ulipristal acetate and mifepristone are used for this condition for 3 to 6 months [6].

h) Gestrinone: It is 19-nortestosterone derivative having anti-estrogenic and anti-progestin activity. It is used in the dose of 2.5 mg twice weekly for 6 months. Danazol was also used for endometriosis in dose of 400 mg to 800 mg daily doses but it is not used as it has got many androgenic side effects and has gone into disrepute [3].

i) Others: TNF-alpha inhibitors, MMP (Matrix Metalloproteinase)-inhibitors, pentoxifylline, raloxifene etc are experimental [7].

Surgical management

Laparoscopic ablation or excision and adhesiolysis improve pregnancy rate in stage I and II endometriosis when compared to diagnostic laparoscopy alone. Operative laparoscopy in stage III and IV endometriosis has shown to improve pregnancy rates as

compared to expectant management [6]. It restores the anatomy of tubes and ovaries and also decreases the inflammatory milieu within the peritoneum and uterus for better implantation rates. When endometrioma or chocolate cyst is present, then cystectomy is preferred to drainage and fulguration as it improves pregnancy rate and also associated with reduced recurrence rates. Cyst wall should be removed completely and cautery should be done to the base of the cyst.

Surgery can also be done by laparotomy as well as laparoscopically. If the patient's age is advanced and she has completed her family with no desire to retain uterus, then hysterectomy with bilateral salpingo-oophorectomy can be offered to woman. Laparoscopic Uterine Nerve Ablation (LUNA) is also an option for endometriosis-associated pain but it has very low efficacy (30% to 40% only) [4]. In DIE, one has to go for radical surgical excision of all deep seated endometriotic lesions with extensive bowel and ureteric dissection [7]. Pre-sacral neurectomy can also be done for transection of presacral nerves but it is obsolete in current practice.

Treatment of Infertility associated with endometriosis: Laparoscopy with treatment of the endometriotic lesions is must. This is followed by ovulation induction and intrauterine insemination in stage I and II diseases. While stage III and stage IV disease patients should undergo ART (Assisted Reproductive Technique) with IVF-ET (*In Vitro* Fertilization-Embryo Transfer) or ICSI (Intracytoplasmic Sperm Injection) [4].

Recurrence: Endometriosis is one disease which is known for high rates of recurrence. The disease recurs in almost 20% of patients in 2 years and 40% recurrence is seen after 5 years [1]. There is high morbidity and surgical complications are also more in recurrent cases. Resistant and repeated cases ultimately require hysterectomy and bilateral salpingo-oophorectomy [6].

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