A REVIEW OF DIAGNOSIS AND PAIN MANAGEMENT OF ENDOMETRIOSIS

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ABSTRACT

Endometriosis is a debilitating condition that is characterized by the presence of endometrial tissue outside the uterus. It affects females in their reproductive years and it is believed to be an estrogen-dependent condition. The estimated prevalence of endometriosis increases in females with subfertility and in the general population is as high as 10%. The diagnosis of endometriosis is usually suspected clinically and confirmed by transvaginal ultrasound or magnetic resonance imaging of the pelvis with the gold standard of diagnosis being the surgical visualization of the pelvic organs by an experienced surgeon during laparoscopy. Diagnosis can be confirmed by positive; however, a negative histology does not exclude it. Serum cancer antigen-125 levels although a poor diagnostic tool in comparison to laparoscopy may be increased in women with endometriosis. Removal of endometriotic implants, removal of nodules or cyst, restoration of normal anatomy, reduction of disease progression and a symptomatic relief are the primary objectives of an intervention. Treatment must be individualized which may require a multidisciplinary approach that involves a pain clinic and counseling services.

Keywords: *Endometriosis, laparoscopy, empirical treatment*

INTRODUCTION

Endometriosis is characterized by the presence of endometrial tissues outside the uterus, affecting females in their reproductive years, and could be an estrogen-dependent condition.[1] Some females with endometriosis are asymptomatic. The estimated prevalence of endometriosis increases in females with subfertility and in the general population is as high as 10%.[2] Patient usually presents with dysmenorrhea, dyspareunia and pelvic pain and sometimes with dyschezia and dysuria, and is usually associated with infertility.[3-6] Although the precise pathogenesis of endometriosis is unclear, it is believed that it may be due to the dissemination of the endometrium to ectopic sites and the resulting establishment of deposits of ectopic endometrium.[7] There are three distinct forms of endometriosis:

(1) endometriotic implants on the surface of pelvic peritoneum and ovaries (i.e., peritoneal endometriosis); (2) ovarian cysts lined by endometrioid mucosa (i.e., endometrioma); and (3) a solid mass comprising endometriotic tissue mixed with adipose and fibromuscular tissue between the rectum and vagina (i.e., rectovaginal endometriotic nodule).[8]

This article aimed to review the current diagnostic methods and the management of endometriosis-associated pain.

Diagnosis:

The diagnosis of endometriosis is usually suspected clinically and confirmed by transvaginal ultrasound or magnetic resonance imaging of the pelvis with the gold standard of diagnosis being the surgical visualization of the pelvic organs by an experienced surgeon during laparoscopy. Diagnosis can be confirmed by positive; however, a negative histology does not exclude it.[9] In patients presenting with dysmenorrhea, noncyclical pelvic pain, deep dyspareunia, infertility, fatigue, dyschezia, dysuria, hematuria, or rectal bleeding, diagnosis of endometriosis should be considered.[4] A clinical examination should be performed in all patients suspected of having endometriosis. Deeply infiltrating nodules are most reliably detected when clinical examination is performed during menstruation.[9] The findings of a fixed retroverted uterus, pelvic tenderness, tender uterosacral ligaments, or adnexal masses support a diagnosis of endometriosis.[4,9] The diagnosis of endometriosis is more apparent if deeply infiltrating nodules are palpated on the rectovaginal wall or visible in the posterior vaginal fornix during clinical examination.[4,9,10] The gold standard test for diagnosing endometriosis is visual inspection of the pelvis during laparoscopy.[4,9] Clinicians should confirm a positive laparoscopy by histology, especially in women undergoing surgery for an ovarian endometrioma and/or deep infiltrating disease so as to identify endometriosis and exclude malignancy.[4,9] Transvaginal sonography is useful for diagnosing or excluding ovarian endometriomas. However, this technique has limited value for diagnosing peritoneal endometriosis.[11] In women with signs and symptoms of bowel endometriosis, transvaginal sonography is useful for identifying or ruling out rectal endometriosis.[12] Transrectal sonography

should be considered with or without barium enema studies to map the extent of bowel wall involvement in women with deep endometriosis. However, it is not possible to conclude to what degree a preoperative barium enema, transvaginal sonography, or transrectal sonography is accurate in the diagnosis of bowel wall involvement in women with deep endometriosis.[13] There is insufficient evidence to support magnetic resonance imaging (MRI) as a useful test to diagnose peritoneal endometriosis. However, MRI may be beneficial for establishing the extent of the disease in women with deep endometriosis.[14]

The level of cancer antigen (CA)-125 may be raised in women with endometriosis. However, CA-125 levels in plasma, urine, or serum should not be used to diagnose endometriosis because it has limited potential with a low sensitivity of 28% and a specificity of 90%.[4,9,15-16] May and colleagues performed a systematic review to assess the clinical significance of all proposed immunological biomarkers for endometriosis and concluded that no marker could conclusively be used to diagnose endometriosis.[17] However, several studies identified endometrial nerve fibers and molecules involved in cell-cycle control, cell adhesion, and angiogenesis as promising options for future biomarker research.

Management of endometriosis-associated pain:

Medical treatment:

Dysmenorrhea, dyspareunia, dysuria, dyschezia, and chronic pelvic pain are endometriosis-associated pain. Empirical treatment of symptoms presumably caused by endometriosis should include detailed counseling and a trial of adequate analgesia, progestogens, or combined oral contraceptive pills.[4,9]. Sufficient evidences are found in support for effective treatment of primary dysmenorrhoea with NSAIDs.[18] Therefore, clinicians should consider the use of NSAIDs or other analgesic drugs to reduce endometriosis-associated pain, after detailed discussion with the patients about the adverse effects commonly associated with the frequent use of these medications.

Hormonal treatment to suppress ovarian function for 6 months reduces endometriosis-associated pain.[9] The evidence is limited, although oral contraceptive pills are commonly used to treat endometriosis-associated pain.

Brown et al[20] concluded in their Cochrane review that sufficient evidence exists to support the effectiveness of progestogens based drugs like medroxyprogesterone acetate, dienogest, cyproterone acetate, norethisterone acetate, or danazol, in reducing pain in women with endometriosis. Danazol should not be used as a first-line drug if there are other medical treatments available because it has severe adverse effects such as acne, weight gain, vaginal spotting, muscle cramps, and irreversible voice change. Dienogest a synthetic oral progestin has no androgenic, glucocorticoid, or mineralocorticoid activity but has strong progestational and moderate anti-gonadotrophic effects. Dienogest is more effective than a placebo in

reducing pelvic pain in patients with a diagnosis of endometriosis.[21] In clinical trials that compared oral dienogest with gonadotropin-releasing hormone (GnRH) agonists for 16 weeks or 24 weeks in women with endometriosis,[22] dienogest was equally effective in reducing pelvic pain, compared with GnRH agonists. Dienogest has fewer hypoestrogenic adverse effects and hence little effect on the bone mineral density; however, it has been associated with a higher incidence of abnormal menstrual bleeding patterns, which usually settles after 90 days of treatment duration and is generally well tolerated by patients.[23] The antiprogestogen gestrinone is an effective therapy for treating painful symptoms associated with endometriosis but in one study, gestrinone resulted in severe androgenic adverse effects (e.g., acne, oily skin, voice change, hair loss) and several patients withdrew from the study.[20] Therefore, women should be counseled about its adverse effects before starting this treatment. Petta and colleagues[24] compared the levonorgestrel-releasing intrauterine system (LNG-IUS) with monthly leuprolide acetate in a randomized, controlled multicenter study and observed no significant reduction in visual analogue pain scores. Gomes et al[25] and Ferreira et al[26] found a significant reduction in pelvic pain scores after 6 months of treatment with no intergroup difference in their study. Thus, it can be concluded that the LNG-IUS appears to reduce endometriosis-associated pain and has a potential benefit because of a better adverse effect profile. In a Cochrane review by Brown et al,[27] a GnRH agonist was more effective than a placebo—but inferior to the LNG-IUS and danazol—in relieving endometriosis-associated pain. In addition, GnRH agonist has a worse adverse effect profile in all reviewed studies.[27] As a result of the hypoestrogenic adverse effects of GnRH agonists, clinicians should prescribe hormonal add-back therapy (i.e., the combination of low dose estrogen and progestogen or tibolone) with the start of the GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.[28–30] Aromatase inhibitors have been studied as a treatment for endometriosis-associated pain in premenopausal women. It has been concluded that, aromatase inhibitors can be used in combination with oral contraceptive pills, progestogens, or GnRH agonists in women with pain from rectovaginal endometriosis that is refractory to other medical or surgical treatment, as they reduce endometriosis-associated pain.[31,32] However, aromatase inhibitors should only be prescribed after patients have had detailed counseling because of their severe adverse effect profile (e.g., vaginal dryness, hot flashes, decreased bone mineral density) and lack of evidence on their long-term effects.

Surgical treatment:

Surgical interventions include elimination of endometriotic lesions via excision, diathermy, or ablation, division of adhesions to restore pelvic anatomy, and interruption of the pelvic nerve pathways to improve pain control.

Crosignani et al[33] showed in a nonrandomized study that laparoscopy and laparotomy were equally effective in the treatment of chronic pelvic pain related to endometriosis. However, laparoscopy is preferred as it is associated with less pain, shorter hospital stay, quicker recovery, and better cosmesis. The Cochrane

review by Jacobson et al[34] showed significant benefits of therapeutic laparoscopy at 6 months and 12 months after surgery. In the five included randomized controlled trials, the methods of treatment included excision, coagulation, or laser vaporization of endometriotic lesions.[34] The reviewers recommend that clinicians should surgically treat lesions when endometriosis is identified at laparoscopy because this treatment effectively reduces endometriosis-associated pain.

Peritoneal endometriosis:

In peritoneal endometriosis, ablation and excision are equally effective in reducing endometriosis-associated pain.[35,36]

Ovarian endometrioma:

Hart et al[37] reviewed two randomized controlled trials revealed a lower recurrence of dysmenorrhea and dyspareunia after cystectomy, compared with drainage and coagulation only, with lower incidence of cyst recurrence. Carmona et al[38] compared cystectomy with carbon dioxide (CO_2) laser vaporization, and concluded that cystectomy is superior to drainage and coagulation or CO_2 laser vaporization with regard to the recurrence of endometriosis-related pain and recurrence of endometriotic cysts.[38] However, it is apt to counsel females that the risk of ovarian failure after bilateral ovarian endometrioma removal is reportedly 2.4% in the literature.[39] Ovarian endometriomas per se may damage ovarian reserve, and cystectomy of endometriomas may cause greater damage to the ovarian reserve in comparison with other benign ovarian cysts. The risk factors associated with surgery-related decline in ovarian reserve include whether the endometriomas were bilateral and size of cyst (greater risk exists for cysts >7 cm). The preoperative serum anti-Mullerian hormone level and age were not risk factors associated with surgery-related decline in ovarian reserve.[40]

Deep endometriosis:

Surgical removal of deep endometriosis via excision can be advocated because it reduces endometriosis-associated pain and improves the quality of life.[41,42] However, this procedure is associated with significant complication rates, especially if it involves the bowel. Deep endometriosis extends beneath the peritoneum and may involve the uterosacral ligaments, pelvic adverse walls, rectovaginal septum, vagina, bowel, bladder, or ureter. Surgical treatment of bowel endometriosis includes superficial shaving, discoid resection, and segmental resection of the bowel to remove the deep endometriosis nodules. Surgical treatment of bladder endometriosis involves excision of the lesion and primary closure of the bladder wall. Ureteral endometriosis lesions may be excised after stenting the ureter; however, in the presence of intrinsic lesions or significant obstruction, segmental excision with end-to-end anastomosis or reimplantation may be

required.

As the last resort to treat endometriosis-associated pain, clinicians should consider hysterectomy with removal of the ovaries and all visible endometriotic nodules in women who have completed their family and failed to respond to more conservative treatments.[4]

The effectiveness of surgical interruption of pelvic nerve pathways to reduce dysmenorrhea was reviewed by Proctor and colleagues[43] in a Cochrane review that included six randomized controlled trials; three trials evaluated the benefit of laparoscopic uterosacral nerve ablation (LUNA) in addition to conservative laparoscopic surgery for endometriosis and the remaining three studies evaluated the effects of presacral neurectomy (PSN) in addition to conservative surgery for endometriosis. The reviewers concluded that LUNA should not be performed as an additional procedure with conservative surgery because it has not been shown to be effective in reducing endometriosis-associated pain. By contrast, PSN is effective as an additional procedure to conservative surgery to reduce endometriosis-associated midline pain; however, it is associated with an increased risk of bleeding and bowel and urinary symptoms.

Furness et al[44] in their Cochrane review concluded that there was no evidence to support the use of preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis. There was similarly no proven benefit of postoperative hormonal treatment within 6 months after surgery because it does not improve the outcome of surgery for pain.

However, for patients not desiring to become pregnant after endometriosis surgery, secondary prevention of dysmenorrhea can be achieved by the postoperative use of a LNG-IUS or by long-term combined oral contraceptives for at least 18–24 months.[45,46]

Nonmedical treatments:

The European Society of Human Reproduction and Embryology (ESHRE) guidelines do not recommend the use of complementary or alternative medicine in the treatment of endometriosis-associated pain because the potential benefits and adverse effects are not well established.[4] These treatments include neuromodulators, nerve blocks, transcutaneous electrical nerve stimulation, acupuncture, behavioral therapy, nutritional supplements, reflexology, homeopathy, traditional Chinese medicine, herbal medicine, sports and exercise. However, the ESHRE Guideline Development Group acknowledges that women with endometriosis who seek complementary and alternative medicine to treat their pain symptoms may benefit from it.

CONCLUSION

To summarize, the primary objectives of interventions include the removal of endometriotic implants, nodules, or cysts, restoration of normal anatomy, reduction of disease progression and symptomatic relief. Treatment must be individualized, and take into consideration the impact of the condition on the quality of life. This may require a multidisciplinary approach that involves treatment at a pain clinic and counseling services.

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