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Review article

## Endometriosis: A review of the diagnosis and pain management

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## ABSTRACT

Endometriosis is characterized by the presence of endometrial tissues outside the uterus. It affects females in their reproductive years, and may be an estrogen-dependent condition. The estimated prevalence of endometriosis in the general population is as high as 10%, and is increased in females with subfertility. The diagnosis of endometriosis is usually suspected clinically and confirmed by transvaginal ultrasound or magnetic resonance imaging of the pelvis. The gold standard of diagnosis is surgical visual inspection of the pelvic organs by an experienced surgeon during laparoscopy. A positive histology will confirm the diagnosis; however, a negative histology does not exclude it. Serum cancer antigen-125 levels may be increased in women with endometriosis, however, it is a poor diagnostic tool in comparison to laparoscopy. The management of endometriosis is dependent on whether the primary problem is pain or subfertility. The primary objectives of an intervention include removing endometriotic implants, removing nodules or cysts, restoring normal anatomy, reducing disease progression, and providing symptomatic relief. Treatment must be individualized and take into consideration the impact of the condition on quality of life. This may require a multidisciplinary approach that involves a pain clinic and counseling services.

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## Introduction

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.<sup>1</sup> Some females with endometriosis are asymptomatic. However, it impacts the physical, mental, and social well-being of many women. The estimated prevalence of endometriosis in the general population is as high as 10%,<sup>2</sup> and is increased in females with infertility.<sup>2</sup> Endometriosis is associated with infertility, although it commonly presents with the symptom of pain in the form of dysmenorrhea, dyspareunia, and pelvic pain.<sup>3,4</sup> Other symptoms include dyschezia in patients with bowel involvement,<sup>4,5</sup> or dysuria in patients with bladder involvement.<sup>4,6</sup>

The precise pathogenesis of endometriosis is unclear, however, this disease may occur because of the dissemination of the

endometrium to ectopic sites and the resulting establishment of deposits of ectopic endometrium.<sup>7</sup> 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).<sup>8</sup>

This article aimed to review the current diagnostic methods and management of endometriosis. This review only covers the management of endometriosis-associated pain. The management of endometriosis-associated infertility is a larger topic and requires a separate review.

## Diagnosis

The diagnosis of suspected endometriosis is based on the clinical history of symptoms, clinical examination, and imaging techniques. A definitive diagnosis of endometriosis can only be determined by the histology of lesions removed at surgery; however, a negative histology does not exclude the diagnosis.<sup>9</sup>

Conflicts of interest: None.

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Clinicians should consider a diagnosis of endometriosis if patients present with dysmenorrhea, noncyclical pelvic pain, deep dyspareunia, infertility, fatigue, dyschezia, dysuria, hematuria, or rectal bleeding.<sup>4</sup> 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.<sup>9</sup> The findings of a fixed retroverted uterus, pelvic tenderness, tender uterosacral ligaments, or adnexal masses support a diagnosis of endometriosis.<sup>4,9</sup> 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.<sup>4,9,10</sup>

The gold standard test for diagnosing endometriosis is visual inspection of the pelvis during laparoscopy.<sup>4,9</sup> 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.<sup>4,9</sup>

Transvaginal sonography is useful for diagnosing or excluding ovarian endometriomas. However, this technique has limited value for diagnosing peritoneal endometriosis.<sup>11</sup> In women with signs and symptoms of bowel endometriosis, transvaginal sonography is useful for identifying or ruling out rectal endometriosis.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup>

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%.<sup>4,9,15,16</sup> May and colleagues<sup>17</sup> performed a systematic review to assess the clinical significance of all proposed immunological biomarkers for endometriosis in the serum, plasma and urine, however, none has been clearly shown to be of clinical use.<sup>17</sup> May and colleagues<sup>15</sup> subsequently performed another systematic review to assess the clinical value of markers derived from endometrial tissue, menstrual fluid, or uterine fluid to diagnose endometriosis noninvasively. They concluded that no marker could conclusively be used to diagnose endometriosis. 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

Endometriosis-associated pain includes dysmenorrhea, dyspareunia, dysuria, dyschezia, and chronic pelvic pain. Empirical treatment of symptoms presumably caused by endometriosis without a prior definitive diagnosis should include detailed counseling and a trial of adequate analgesia, progestogens, or combined oral contraceptive pills.<sup>4,9</sup> Empirical treatment is advocated because of the invasiveness of laparoscopy and the ease of prescribing these drugs. However, other causes of pelvic pain symptoms should be excluded before starting an empirical treatment.

The effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) in treating endometriosis-associated pain is not well

established because of the lack of studies.<sup>4,9</sup> However, there is sufficient evidence to support that NSAIDs effectively treat primary dysmenorrhea.<sup>18</sup> Therefore, clinicians should consider NSAIDs or other analgesic drugs to reduce endometriosis-associated pain, after discussing with women 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.<sup>9</sup> In a Cochrane review,<sup>19</sup> only one study was found that included the use of hormonal contraceptives in the treatment of pain in women with endometriosis. The evidence is limited, although oral contraceptive pills are commonly used to treat endometriosis-associated pain; they can also serve as contraception, regulate the menstrual cycle, and have a long-term safety profile.

Brown et al<sup>20</sup> concluded in their Cochrane review that sufficient evidence exists to support the effectiveness of progestogens in reducing pain in women with endometriosis. This group of drugs includes medroxyprogesterone acetate, dienogest, cyproterone acetate, norethisterone acetate, or danazol. Clinicians should consider the adverse effect profiles of these medications and tailor treatment to improve the quality of life of a woman. In this respect, 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 (Visanne; Bayer Healthcare, Berlin, Germany) is a synthetic oral progestin with strong progestational and moderate anti-gonadotrophic effects, however, it has no androgenic, glucocorticoid, or mineralocorticoid activity. A randomized clinical trial indicated that oral dienogest is more effective than a placebo in reducing pelvic pain in patients with a diagnosis of endometriosis.<sup>21</sup> In clinical trials that compared oral dienogest with gonadotropin-releasing hormone (GnRH) agonists for 16 weeks or 24 weeks in women with endometriosis,<sup>22</sup> 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.<sup>23</sup>

The antiprogestogen gestrinone is an effective therapy for treating painful symptoms associated with endometriosis. Gestrinone was studied in four randomized controlled trials and proven to reduce pelvic pain, dysmenorrhea, deep dyspareunia, and nonmenstrual pain.<sup>20</sup> 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. Hence, women should be counseled about its adverse effects before starting this treatment.

Petta and colleagues<sup>24</sup> compared the levonorgestrel-releasing intrauterine system (LNG-IUS) with monthly leuprolide acetate in a randomized, controlled multicenter study that involved 83 patients with endometriosis. After 6 months of treatment, both groups had significantly reduced visual analogue pain scores, however, no difference existed between the groups. Gomes et al<sup>25</sup> and Ferreira et al<sup>26</sup> used a similar regimen, as described previously, and found a significant reduction in pelvic pain scores after 6 months of treatment; however, there was no intergroup difference in either study. With these data, 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,<sup>27</sup> 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.<sup>27</sup>

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.<sup>28–30</sup> However, because of the lack of large randomized controlled trials, it remains unclear which type of add-back therapy should be used. Because of the severe adverse effects of GnRH agonists, women should be counseled in detail before starting this treatment.

Aromatase inhibitors have been studied as a treatment for endometriosis-associated pain in premenopausal women. The authors of two systematic reviews concluded that, in women with pain from rectovaginal endometriosis that is refractory to other medical or surgical treatment, aromatase inhibitors can be used in combination with oral contraceptive pills, progestogens, or GnRH agonists because they reduce endometriosis-associated pain.<sup>31,32</sup> 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

In recent decades, laparoscopy has dominated over open surgery in the management of endometriosis. This includes 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<sup>33</sup> 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 associated with less pain, shorter hospital stay, quicker recovery, and better cosmesis; therefore, it is preferred to laparotomy. The Cochrane review by Jacobson et al<sup>34</sup> 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.<sup>34</sup> 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.<sup>35,36</sup> However, this conclusion is derived from one small study and a larger study with suboptimal design. Hence, this finding should be treated with caution.

### Ovarian endometrioma

Hart et al<sup>37</sup> reviewed two randomized controlled trials that compared laparoscopic excision of ovarian endometriotic cysts ( $\geq 3$  cm) with drainage and coagulation by bipolar diathermy. Both studies revealed a lower recurrence of dysmenorrhea and dyspareunia after cystectomy, compared with drainage and coagulation only. In addition, the rate of cyst recurrence was lower with the excisional approach.

Carmona et al<sup>38</sup> compared cystectomy with carbon dioxide (CO<sub>2</sub>) laser vaporization, and found the recurrence of cysts were more common at 12 months after laser vaporization (but not at 60 months). The time to recurrence was also shorter postlaser vaporization in comparison with cystectomy.<sup>38</sup> Hence, it can be concluded that cystectomy is superior to drainage and coagulation or CO<sub>2</sub> laser vaporization with regard to the recurrence of

endometriosis-related pain and recurrence of endometriotic cysts. 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.<sup>39</sup>

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.<sup>40</sup>

### Deep endometriosis

Surgical removal of deep endometriosis via excision can be advocated because it reduces endometriosis-associated pain and improves the quality of life.<sup>41,42</sup> 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.<sup>4</sup>

The effectiveness of surgical interruption of pelvic nerve pathways to reduce dysmenorrhea was reviewed by Proctor and colleagues<sup>43</sup> 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<sup>44</sup> 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.<sup>45,46</sup>

### 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.<sup>4</sup> These treatments include neuro-modulators, 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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