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Endometriosis: *Current Commentary*

Optimal Management of Endometriosis and Pain

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The pathophysiology of endometriosis-associated pain involves inflammatory and hormonal alterations and changes in brain signaling pathways. Although medical treatment can provide temporary relief, most patients can achieve long-term sustained pain relief when it is combined with surgical intervention. Owing to its complexity, there is an ongoing debate about how to optimally manage endometriosis-associated pain. We believe optimal management for this condition requires: 1) possible egg preservation in affected young patients with and without endometriomas; 2) preoperative medical suppression to inhibit ovulation and to avoid removal of functional cysts that might look like endometriomas; and 3) postoperative hormonal suppression to decrease recurrence, but this treatment should be modified according to disease severity, symptoms, and fertility goals.

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Endometriosis is a hormone-dependent progressive inflammatory disorder that develops when endometrial-like tissue is formed outside of the uterine cavity. Chronic pain, infertility, and organ dysfunction are the key clinical features.[1,2] Approximately 5–10 million reproductive-aged women in the United States suffer from endometriosis–the great imposter.[2] Because of its complex nature, it can take 6–10 years to diagnose endometriosis, and its symptomatology varies tremendously.[1,2] Most patients experience cyclic pelvic pain with menses, but some experience symptoms of noncyclic pelvic pain, such as dyspareunia, dyschezia, and dysuria. Characteristically, pain severity does not correlate with the amount of endometrial tissue formed. Many patients present only with unexplained infertility. As Giudice states, "infertility results from the toxic effects of the inflammatory process on gametes and embryos, compromised fimbrial function, and eutopic endometrium that is resistant to the action of progesterone and is inhospitable to embryonic implantation."[3] However, endometriosis can produce symptoms that mimic other diseases, including irritable bowel syndrome; interstitial cystitis; vascular, musculoskeletal, neurologic, and psychological diseases; obesity; anorexia; thyroid dysfunction; autoimmune disorders; and heart disease.

The etiology of endometriosis is still not fully understood, but estrogen plays a major role in its pathogenesis. A commonly accepted theory that endometriosis is caused by retrograde menstruation was introduced in the 17th century by Ruysch, and this was later supported by Sampson.[2] In the early 1900s, Thomas Cullen recognized that endometriosis could invade pelvic nerves.[2] One theory is that endometrial-like tissue enters the peritoneal cavity through the fallopian tubes, and this ectopic tissue persists by establishing its own blood supply to ensure its survival and create a protective environment to prevent the immune system from clearing the ectopic tissue. In fact, the implant can attract inflammatory

cells, which further potentiates its growth. Moreover, this ectopic endometrial-like tissue is biologically active outside of the uterus.[3]

ENDOMETRIOSIS-ASSOCIATED PAIN

The pelvis is highly vascularized and enervated, which is why pain impulses from this region are processed and sent to the brain (Fig. 1).[4–6] This, along with multiple other factors, contributes to the pain syndrome that is associated with endometriosis. Peritoneal fluid in women with endometriosis contains high levels of nerve growth factors that promote neurogenesis, the ratio of sympathetic and sensory nerve fibers is significantly altered within endometriotic tissue, and the nerve density within endometriotic nodules is increased.[7,8] Also, the cytokines and prostaglandins produced by mast cells and other inflammatory cells attracted to ectopic endometrial-like tissue can activate nerve fibers and can trigger nearby cells to release inflammatory molecules.[5,6,8,9]

Another source of pain is nerve fiber entrapment within endometriotic implants.[4] The cyclical sciatic pain, weakness, and sensory loss can all stem from endometriotic entrapment of the sciatic, femoral, or lumbosacral nerve roots.[9] There are numerous descriptions of sacral radiculopathy occurring in patients with endometriosis, and there are even descriptions of wheelchair-bound patients becoming fully ambulatory after treatment of infiltrative endometriosis.[9]

Central sensitization is another mechanism that promotes endometriosis-associated pain. Patients become highly sensitive to subsequent painful stimuli because of endometriosis-induced neuroplastic changes in descending pathways that modulate pain perception.[10] In response to a subsequent insult (ie, nephrolithiasis or peritoneal organ injury), women can experience pain from endometriosis as a result of inability to engage descending inhibition pathways.[10]

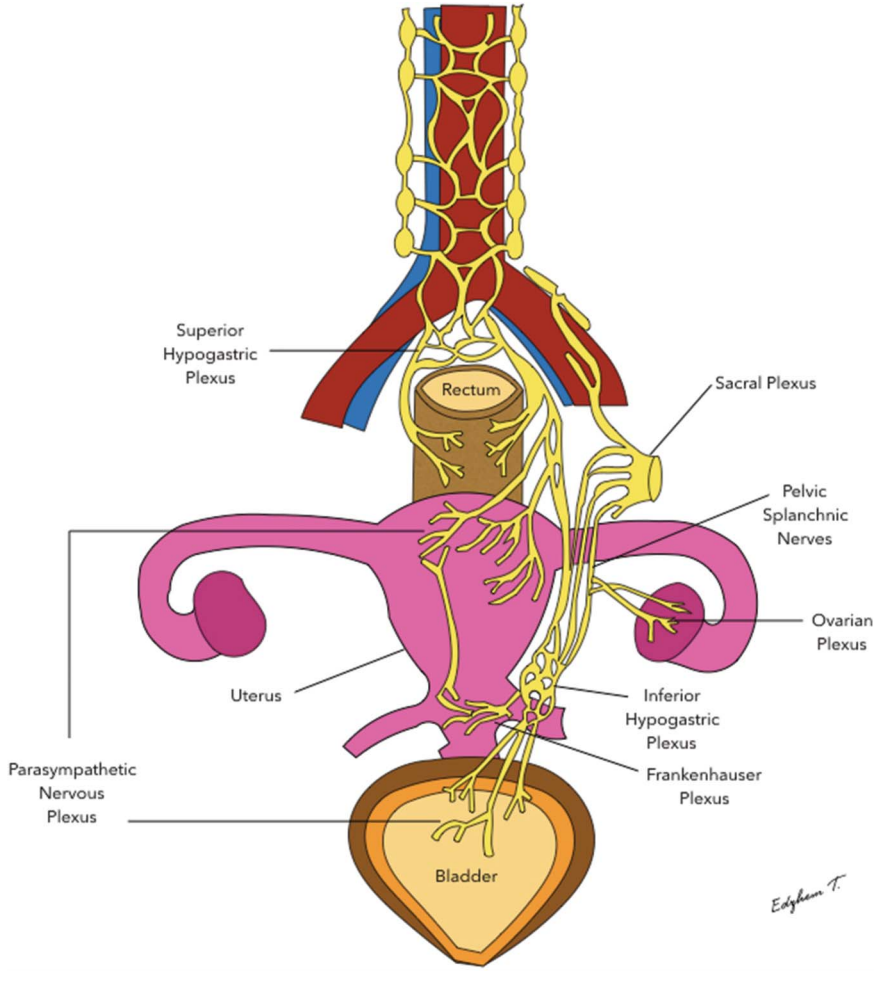

Fig. 1. Pelvic nerve supply. Superior hypogastric plexus, which contains sympathetic and sensory afferent fibers from the uterus, is an extension of the aortic plexus at the fifth lumbar vertebra. This plexus divides into right and left hypogastric nerves that join the pelvic splanchnic nerves from S2-S4. Pain impulses from the uterus and cervix travel through afferent sympathetic nerves, which are found in the uterosacral ligaments and posterolateral pelvis. These coalesce in the midline as the superior hypogastric plexus and travel to the dorsal root ganglia of the spinal cord. These pain stimuli are then processed and sent to the brain. Illustration by Edzhem Tombash and Camran Nezhat. Used with permission. (Adapted by permission from Springer Nature: Nezhat C, Falik R, McKinney S, King LP. Pathophysiology and management of urinary tract endometriosis. Nat Rev Urol 2017;14(6):359–72. Copyright 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.)

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MEDICAL MANAGEMENT

Pain management should be individualized. The goal of medical therapy is to reduce pain by decreasing inflammation as well as ovarian and local hormone production (Table 1). Complete estrogen suppression may not be necessary to relieve endometriosis-associated pain.[11] Medical treatment is usually not curative but suppressive, and symptoms will often recur after therapy discontinuation. The recurrence rate of endometriosis is highly variable, ranging from 4–74%.[2,3]

Initial treatment is typically use of combined oral contraceptive pills, which are effective in decreasing pain as well as in preventing postoperative recurrence.[12] For those who cannot tolerate or have contraindications to estrogen, progestins such as medroxyprogesterone acetate, norethindrone acetate, or levonorgestrel are indicated. However, there are patients who have decreased receptor sensitivity as a result of aberrant gene expression in the eutopic endometrium that leads to progesterone resistance.[13] For those unable to tolerate oral medications, the levonorgestrel-releasing intrauterine system can reduce pain and recurrence.[4,14] However, the levonorgestrel-releasing intrauterine system does not inhibit ovulation and the recurrence of endometriomas. For those patients for whom the previous options have failed, we recommend using a gonadotropin-releasing hormone (GnRH) agonist with add-back therapy to prevent bone loss and to ease side effects. Patients taking GnRH agonists for endometriosis may develop resistance, because endometrial-like tissue expresses aromatase and produces its own estradiol.

Our experience is mixed with GnRH antagonists, aromatase inhibitors, and bazedoxifene along with conjugated estrogens. Some patients obtain pain relief

Table 1. Medical Treatment Options for Endometriosis-Associated Pain

Medication	Characteristics	Side Effects
Combined OCPs	1st-line Oral, patch, ring Continual use (skip 7-d placebo) Temporary relief, inexpensive Decreases pain by 52% Limited use in patients with migraines Continual use decreases recurrence of pain after surgical excision	Thrombotic risk, nausea, weight gain, breakthrough bleeding, depression, breast tenderness, headache, amenorrhea
Progestins	Oral, depot injections, implant, IUD Temporary relief, inexpensive Decreases severity of diarrhea, intestinal cramping, and passage of mucus in colorectal endometriosis Decreases deep dyspareunia Develops resistance IUD insertion decreases pain after surgical treatment	Weight gain Decreased libido Depression Fluid retention
GnRH agonists	2nd-line, must have diagnostic workup before administration Depot injection, expensive Temporary relief Limited use up to 1-y with add-back therapy Improves pain scores 60–100% 53% recurrence of symptoms after 2 y	Changes lipid profile, depression, hot flushes, bone loss, urogenital atrophy
Aromatase inhibitors	Not FDA approved Use for those for whom other therapies have failed Major side effects Limited duration	Hot flushes, myalgia, arthralgia
GnRH antagonists	Oral administration, expensive Use limited to 6 mo Improves dyspareunia and dysmenorrhea	Mood changes, hot flushes, loss of libido, vaginal dryness, mild decrease in axial bone density

OCP, oral contraceptive pill; IUD, intrauterine device; GnRH, gonadotropin-releasing hormone; FDA, U.S. Food and Drug Administration.

from these medications, but others discontinue them prematurely owing to high expectations of fast mitigation of symptoms.

Since use was legalized in California, tetrahydrocannabinol and cannabidiol, either separately or in combination, present an alternative option. Patients frequently prefer these compounds over opioids, and their use is associated with less nausea and constipation. The use of tetrahydrocannabinol or cannabidiol is especially beneficial for managing postoperative pain, and their use does not have the addictive concerns associated with opioid use. We use an enhanced recovery after surgery protocol and highly discourage opioid use.

Acupuncture is another potentially useful adjunct in treating the pain. It has been proposed to work by activating descending inhibitory pain pathways while centrally deactivating pain signals. Acupuncture also increases the pain threshold and leads to production of neurohumoral factors such as dopamine, nitric oxide, noradrenaline, acetylcholine, and others.[15] In addition, it increases natural killer cells, thereby modifying immune function and decreasing estrogen production.[15]

Pelvic physical therapy has been shown in a retrospective study to improve endometrial pain in 63% of patients after at least six sessions.[4] Deep pressure massage, stretching pelvic floor muscles, joint mobilization, foam rollers with breathing, and relaxation techniques are the integral elements.

SURGICAL MANAGEMENT

Surgery remains the mainstay in definitive diagnosis. High-definition video laparoscopy with or without robotic assistance is the standard initial approach. In our extensive experience, laparotomy is seldom necessary. Excellent illumination with enhanced video magnification enables better recognition of subtle lesions as well as the depth of infiltrative lesions. Depending on the patient's desire, location of lesion, availability of proper instrumentation, as well as the experience and skill of the surgeon, eradication of endometriosis can be achieved with surgical management techniques that include excision, vaporization, and ablation. The nonsurgical options discussed above can be used to supplement surgical treatment for long-term results.[4]

The best surgical approach for the treatment of superficial endometriosis is controversial. A meta-analysis of randomized controlled trials involving 335 women demonstrated that excision of endometriosis was superior to coagulation in reducing dysmenorrhea, dyschezia, and chronic pelvic pain when evaluated at 12 months of follow-up.[16] Laser ablation with layer-by-layer vaporization of endometriosis was shown to be 65% effective in reducing pain, compared with the 22% reduction when diagnostic laparoscopy alone was performed.[16]

Laparoscopic uterosacral nerve ablation to disrupt efferent nerve fibers has been tested. However, multiple large randomized controlled trials did not find it to be beneficial in reducing endometriosis-associated pain. Complications of subsequent uterine prolapse and intraoperative ureteral transection have been reported with this procedure.[16] In contrast, laparoscopic presacral neurectomy was 87% efficacious in reducing severe midline pelvic pain.[2,4–6] We find this procedure especially effective in patients with mild or no endometriosis.[17] The adverse effects associated with presacral neurectomy are constipation and bladder and urinary symptoms.[17] We perform presacral neurectomy in only about 1% of our patients.

A prospective, multicenter cohort study of 981 women with varying degrees of disease showed significant postsurgical symptom improvement over 36 months in patients who underwent laparoscopic excision of endometriosis. The most notable improvement was seen in dysmenorrhea, with a 57% reduction in symptoms; chronic pelvic pain and dyspareunia were reduced by 30%. Owing to recurrent pain, a second-look surgery was performed in 9% of patients, and histologically confirmed endometriosis recurrence was documented in 5%. Of these patients, 7% benefited from medical therapy.[18]

Abbott et al demonstrated significant pain relief (80%) after surgery compared with a placebo group (32%). They report progression of disease with second-look laparoscopy in 45%, no change in 33%, and improvement in 22% of patients. Twenty percent of cases were not responsive to surgery.[18]

Several noninvasive diagnostic tests for endometriosis, such as BCL6 and endometrial function tests and blood and saliva tests, are becoming available. These tests are especially important for asymptomatic infertility patients and for younger patients, for whom we recommend egg preservation if possible. We individualize management of ovarian endometriosis and endometriomas based on the patient's age, fertility desires, family history of ovarian cancer, and type of endometriomas.[4] For many infertility patients, restoration of anatomy along with methodical and meticulous treatment of endometriosis can lead to natural conception or increase in overall in vitro fertilization success.[19] The treatment of endometriosis needs to be thorough to be effective. We recommend preoperative medical suppression to inhibit ovulation and to avoid removal of functional cysts that might look like endometriomas and possibly decrease inflammation.

We prefer conservative treatment for lesions of the rectum and rectal bulb close to the anal verge with associated sympathetic and parasympathetic nerve involvement. This can be accomplished by shaving excision and disc resection rather than through segmental resection (Fig. 1).[5] Injury to the neurovascular structures could lead to gastrointestinal and genitourinary (GU) complications such as severe constipation, urinary retention, and loss of bowel or bladder function (Fig. 1).[5,6]

Untreated endometriosis of the GU system can have dire side effects, such as silent kidney loss.[6] Radical surgical management of problematic GU endometriosis may require segmental bladder resection, ureterolysis, ureteral resection and reanastomosis, and ureteroneocystostomy with or without psoas hitch (Fig. 1).[6]

For the perimenopausal patient who has completed childbearing but still desires conservative treatment, we recommend surgical treatment of endometriosis as well as endometrial ablation with salpingectomy to prevent future pregnancy and reduce the risk of ovarian and fallopian tube cancer. We also recommend postoperative medical therapy and long-term follow-up to monitor for recurrence. For patients who do not desire future fertility and have debilitating symptoms for which other therapies have failed, we discuss the risk/benefit ratio of a hysterectomy with bilateral salpingectomy as well as postoperative medical suppression to mitigate recurrence. We inform patients that ovarian conservation is not optimally effective owing to continued hormonal stimulation of microscopic endometriotic lesions. However, in a young patient, bilateral salpingo-oophorectomy in addition to hysterectomy without hormone therapy may lead to early-onset cardiovascular disease, osteoporosis, and urogenital atrophy. In patients with catamenial pneumothorax associated with thoracic endometriosis, we recommend bilateral salpingo-oophorectomy when they have completed childbearing and when risks of videothoracoscopy outweigh the benefits.[4,20] Management of surgical menopause with estrogen alone can stimulate growth of endometriosis. Patients who have undergone hysterectomy with bilateral salpingo-oophorectomy with subsequent adjuvant combined estrogen and progesterone for endometriosis suppression were found to have a low risk (4%) of recurrence.[20] On the contrary, when progesterone is not used, the recurrence of endometriosis is 5–15%.[2,3]

If removal of the uterus is indicated, we favor a total hysterectomy over a supracervical approach. The rationale lies in the evidence of abnormally increased nerve density in the endometrial implants in the cervix. Up to one quarter of patients will undergo subsequent trachelectomy owing to pelvic pain or bleeding after hysterectomy. Tsafrir et al[21] demonstrated that the most common pathologic diagnosis and indication for trachelectomy was endometriosis. In a retrospective review after supracervical hysterectomy, 18% of patients reported pelvic pain and 10% reported dyspareunia related to the remaining cervix. These patients ultimately underwent trachelectomy.[22] In a review of trachelectomy samples, higher cervical nerve fiber density was found in women for whom pelvic pain was the procedure indication compared with the control group who had nonpain indications.[22] Laparoscopic trachelectomy is indicated for endometriosis patients with persistent pelvic pain after supracervical hysterectomy.[23]

Though deeply infiltrative endometriosis can invade the superior and inferior hypogastric plexus, as well as the sympathetic and parasympathetic nerve bundles, surgical injury can lead to even more devastating effects. We use the Tokyo method to preserve nerves supplying the bowel, bladder, and sexual organs. This nerve-sparing technique includes separation and ligation of the vascular portion of the cardinal ligament while preserving the branches of the pelvic splanchnic nerves (Fig. 1).[5,6] We have previously suggested leaving some rectal disease behind and opting for postoperative hormonal suppression. This decreases the risk of injuring the rectum or its neurovascular bundle, which would necessitate a permanent colostomy (Fig. 1).[5]

Surgical treatment of endometriosis can be challenging owing to its highly vascularized, deeply invasive nature. Endometriosis can distort the anatomy, leading to indistinct planes of dissection. To treat patients adequately, the surgeon must be comfortable dissecting the retroperitoneal spaces. From our experience, it is evident that hormonal suppression may decrease inflammation, allowing for less bloody dissection and optimization of lesion excision. We therefore recommend some form of temporary hormonal suppression before surgery for patients with advanced endometriosis.[24]

Postoperatively, these patients will still need an individualized hormonal treatment plan to prevent microscopic or residual endometriosis from flourishing. Gonadotropin-releasing hormone agonists and progestins have been shown to significantly reduce pain.[14] Postoperative hormone therapy should include both estrogen and progestogen, because estrogen alone may stimulate growth of microscopic disease.

In summary, endometriosis is a lifelong disease that can affect almost every organ in the body. The hormonal imbalance and the proinflammatory milieu alter neuronal signaling systems, which can alter pain processing. An individualized approach is required for the initial pharmacologic plan, and this should be included in the perioperative treatment plan. Although rare, the risk of cancer arising from endometriosis warrants close monitoring.[25] The complex and multifactorial nature of endometriosis requires a multidisciplinary approach to treatment. A combination of medical, surgical, psychotherapeutic, and alternative treatments can improve quality of life for women who suffer from endometriosis. Currently available knowledge and advanced surgical techniques can be used to reduce the torment and suffering of those afflicted with endometriosis.

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