Treatment of pelvic pain associated with endometriosis: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

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Pain associated with endometriosis may involve many mechanisms and requires careful evaluation to confirm the diagnosis and exclude other potential causes. Both medical and surgical treatments for pain related to endometriosis are effective, and choice of treatment must be individualized. This document replaces the document by the same name last published in 2008 (Fertil Steril 2008;90:S260–9). (Fertil Steril® 2014;101:927–35. ©2014 by American Society for Reproductive Medicine.)

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Endometriosis is one of the most common gynecologic disorders and is found in 70%–90% of patients with pelvic pain symptoms (1, 2). Women with endometriosis have an increased risk of abdominopelvic pain, dysmenorrhea, and dyspareunia compared with controls without endometriosis (3). The evaluation of pain from endometriosis and its response to treatment are made difficult by [1] methodologic difficulties in measuring pain; [2] incomplete understanding of the mechanism by which endometriosis causes pain; [3] difficulty in determining the success of medical and surgical therapies compared with placebo; [4] the tendency for chronic pain to progressively involve surrounding organ systems beyond the reproductive tract; and [5] pain attributed to endometriosis when other coexisting conditions may be the true cause of pain. This document addresses endometriosis and associated pelvic pain and outlines treatment options.

DIFFERENTIAL DIAGNOSIS OF PELVIC PAIN

Conditions of the reproductive tract that can cause chronic pelvic pain include not only endometriosis, but also adenomyosis, pelvic adhesions, pelvic inflammatory disease, congenital anomalies of the reproductive tract, and ovarian or tubal masses. Pelvic pain, however, is not necessarily due to gynecologic causes. It can be caused by disorders in the gastrointestinal, urinary, neurologic, and musculoskeletal systems and also may be a manifestation of psychological or psychiatric disorders. Common nongynecologic causes of pelvic pain may include irritable bowel syndrome, interstitial cystitis, fibromyalgia, and musculoskeletal disorders such as trigger point pain and pelvic floor dysfunction (4). It may be difficult to distinguish endometriosis from these conditions because the symptoms may be similar, occurring in a cyclic or constant pattern. A thorough evaluation to exclude other causes of pelvic pain should be pursued before aggressive therapy and also in those women who do not respond to conventional therapy for endometriosis.

MECHANISMS OF PAIN FROM ENDOMETRIOSIS

Endometriosis can appear in different forms in the female pelvis, including clear vesicles, red flame lesions, dark pigmented lesions with hemosiderin, and white scarring, each of which may contribute to pain by different mechanisms. Although, in general, there is no established relationship between the extent of disease and symptoms, the location and type of the disease can impact pelvic pain (5). Although considered a progressive disease, endometriosis also can remain static and even regress without treatment (6). The three most commonly suggested mechanisms for pain production in endometriosis are [1] production of substances such as growth factors and cytokines by activated macrophages and other cells associated with functioning endometriotic

implants (7, 8); [2] the direct and indirect effects of active bleeding from endometriotic implants; and [3] irritation of pelvic floor nerves or direct invasion of those nerves by infiltrating endometriotic implants, especially in the cul-de-sac (8, 9). It remains plausible that in any individual more than one or all of these mechanisms may be in operation. The neural irritation or invasion hypothesis has gathered much support in the past decade. Tender nodularity in the region of the cul-de-sac and the areas of the uterosacral ligaments has approximately 85% sensitivity and 50% specificity for the diagnosis of infiltrative endometriosis (10). Women with such findings on pelvic examination may have deep dyspareunia and more severe dysmenorrhea. Those with infiltration of the uterosacral ligaments and/or diseases directly adjacent to or invading the rectal wall may have dyschezia (9). The intensity of pain associated with infiltrative disease has been correlated with the depth of penetration of the lesion. The most severe pain is seen when the disease extends ≥ 6 mm below the peritoneal surface (10). Both perineural inflammation and direct infiltration of nerves by endometriosis have been observed (11). However, these kinds of perineural changes have been observed most commonly in women with central pelvic disease (i.e., around the uterosacral ligaments and in the cul-de-sac and not in those with lateral peritoneal or ovarian endometriosis).

Pain Measurement

Assessing the level of pain in an individual can be difficult. Most clinical studies of pain use standardized methods, which are not used in clinical practice, such as a visual analog scale (rating pain from "none" to "worst ever") (12), the McGill Pain Questionnaire (13, 14), or a unique, simple categorical scale (15). Quality-of-life scales, such as the SF-36 (16), also are used to assess the impact of pain and the response to treatment.

Impact of the Gonadal Steroids on Pain

Estrogen (E) is believed to decrease pain perception (increase pain threshold), at least at a somatic level. A meta-analysis of 16 studies of experimentally induced pain demonstrated that somatic sensory pain thresholds were lower by approximately 30% in the immediately premenstrual and menstrual phases of the cycle when E levels are low (7). This observation is consistent with the documented phenomenon of increased symptoms of irritable bowel syndrome immediately before and during menses, although bowel motility does not seem to change measurably in women with irritable bowel syndrome during these time periods (17, 18). Progesterone also has an impact on pain, as evidenced by a general dampening effect on neuronal activity seen with the use of high-dose progestogens (19). On the other hand, E also increases pain associated with endometriosis by directly stimulating growth of the lesions. Endometriotic lesions demonstrate variable levels of E (ER) and P receptors (PR) and hormonal responsiveness (10). Clinically, this correlates with worsening pain symptoms in women of reproductive age and improvement at menopause and in medically induced hypoestrogenic states. In addition, endometriotic tissue has been found to exhibit a high level of aromatase activity, which causes a local accumulation of estradiol and stimulates growth of the tissue (20). This observation may help explain persistent or recurrent disease in E-deficient states (21).

DIAGNOSIS

The intensity and character of the pain associated with endometriosis rarely correlate with the severity of disease, and cyclic pain does not always indicate endometriosis (2, 5). Pelvic examination is notoriously inaccurate in estimating the volume of endometriosis, and roentgenographic, ultrasound, and magnetic resonance imaging (MRI) techniques have not improved the diagnostic accuracy. Operative visualization of characteristic lesions generally is considered an acceptable surrogate for excision with histologic diagnosis of endometriosis (22). Atypical lesions, including those within peritoneal pockets, are more difficult to characterize without biopsy (23, 24). Although studies suggest that microscopic endometriosis may routinely elude detection at laparoscopy (25, 26), it is believed that these forms of the disease may play a lesser role, if any, in the pain associated with endometriosis (24). Once endometriosis has been diagnosed, progression of the disease is not reliably assessed by pain symptoms or radiologic tests. Gonadotropin-releasing hormone agonists (GnRH-a) have been advocated to diagnose and treat endometriosis without performing laparoscopy, based primarily on the results of 1 study involving 95 women with moderate-to-severe chronic pelvic pain unrelated to menstruation who were randomized to receive leuprolide acetate (LA) for depot suspension 3.75 mg or placebo injection monthly for 3 months after laparoscopy (27). The underlying premise was that improved pain symptoms during the hypoestrogenic state induced by GnRH-a treatment might reliably indicate that endometriosis was the cause (28, 29). However, pain relief in response to LA for depot suspension was not significantly different in those who did or did not have detectable endometriosis at laparoscopy (81.8% vs. 72.7%, respectively). Therefore, the response to LA for depot suspension did not accurately diagnose endometriosis. Treatment with LA for 3 months did improve dysmenorrhea, pelvic pain, and dyspareunia, regardless of the presence or absence of endometriosis. Establishing the correct diagnosis by laparoscopy before initiating therapy with medication that is associated with significant short-term and long-term side effects is the preferred approach, although further studies are warranted.

SURGICAL THERAPY FOR ENDOMETRIOSIS

A Cochrane meta-analysis of 5 randomized controlled studies evaluating laparoscopic treatment of endometriosis compared with diagnostic laparoscopy without treatment reported that pain was significantly improved in the treatment group (30). The proportion of patients with improved pain symptoms was significantly higher among those with moderate and mild endometriosis (~100% and ~70%, respectively) than in women with minimal disease (~40%) (31). Pain recurrence after repeat surgery for recurrent disease ranges from

20%–40%, similar to primary surgery (32). One study evaluated repeat laparoscopy in patients who were still symptomatic 1 year after the initial surgery. Of those, 29% showed disease progression, 29% showed disease regression, and in the remaining 42% disease was unchanged (6). A retrospective study evaluating the occurrence of subsequent surgery after laparoscopic treatment of endometriosis for pain found 79.4%, 53.3%, and 44.6% remained surgery-free at 2, 5, and 7 years, respectively (33). Taken together, these observations indicate that laparoscopic treatment of endometriosis does lead to improvement in disease and pain and thus supports the recommendation to treat endometriotic lesions at the time of diagnostic laparoscopy. Surgical options for the treatment of endometriosis include the use of unipolar or bipolar cautery, laser ablation using potassium-titanyl-phosphate, carbon dioxide, or neodymium: yittrium, aluminum, garnet lasers, and excision techniques. Each has advantages and disadvantages with respect to lesion removal, tissue trauma, and bleeding. The only adequately powered, randomized study comparing excision versus ablation found no significant difference in pain scores up to 1 year after surgery. In addition, the results were not influenced by the stage of disease or whether the lesions were superficial or deep (34).

Ovarian Endometriomas

Medical therapy for ovarian endometriomas may lead to a temporary reduction in size of the cysts but not complete resolution. Surgery is therefore the primary approach for symptomatic or large endometriomas (35). Conservative surgical options include excision of the cyst wall, drainage and coagulation/ablation of the cyst, and simple drainage of the cyst. Cyst excision is more effective than fenestration and ablation of the cyst wall in terms of reduced reoperation rates and more improvements in symptoms of dysmenorrhea, deep dyspareunia, and nonmenstrual pain (36–38). However, with cyst excision there is concern about the risk of ovarian damage and impaired ovarian reserve. A meta-analysis of 8 studies of ovarian cystectomy for endometriomas found significantly lower antimüllerian hormone levels postoperatively (-1.13; 95% confidence interval [CI] -0.36 to -1.88) (39). Simple drainage of endometriomas is associated with a high risk of cyst recurrence (80%–100%) within 6 months and therefore is not recommended as definitive therapy (40–42).

Laparoscopic Uterosacral Nerve Ablation

Laparoscopic uterosacral nerve ablation is a technique designed to disrupt the efferent nerve fibers in the uterosacral ligaments to decrease uterine pain for women with intractable dysmenorrhea (43, 44). However, a large randomized, controlled trial comparing results of conservative laparoscopic surgery for endometriosis with conservative surgery with laparoscopic uterosacral nerve ablation observed no difference between groups in the proportions of patients having recurrent dysmenorrhea 1 and 3 years after surgery (45). Currently, laparoscopic uterosacral nerve ablation does not appear to offer any added benefits beyond those that can be achieved with conservative surgery for endometriosis alone. Although laparoscopic uterosacral nerve ablation has a low risk of complications, uterine prolapse and transection of the ureter have been reported (46).

Presacral Neurectomy

Presacral neurectomy involves interrupting the sympathetic innervation to the uterus at the level of the superior hypogastric plexus. One randomized, controlled trial involving 71 women demonstrated that presacral neurectomy at the time of conservative surgery for endometriosis decreased midline dysmenorrhea but did not improve other symptoms of dysmenorrhea, dyspareunia, or pelvic pain (47). Another randomized, controlled trial involving 141 women compared results achieved with conservative laparoscopic surgery for endometriosis with and without presacral neurectomy. In this study, the women who underwent presacral neurectomy experienced significantly more improvements in dysmenorrhea, dyspareunia, and pelvic pain 6 and 12 months after surgery compared with women treated by conservative surgery alone (48). Presacral neurectomy has been proposed for the treatment of midline pain associated with menses because its effects on other components of pelvic pain have been inconsistent. However, it is important to recognize that presacral neurectomy is a technically challenging procedure associated with significant risk of bleeding from the adjacent venous plexus. Patients may also experience constipation and/or urinary retention postoperatively.

Hysterectomy

Hysterectomy with bilateral salpingo-oophorectomy (BSO) generally is reserved for women with debilitating symptoms attributed to endometriosis who have completed childbearing and in whom other therapies have failed. The success of this approach is attributed to debulking the disease with the resulting surgical menopause causing atrophy of endometriotic tissue. Hysterectomy without BSO is less effective, as disease recurrence and subsequent reoperation rates are higher (32, 33, 49). The decision to proceed with BSO at the time of hysterectomy for endometriosis and pain should take into consideration the consequences of surgical menopause compared with the potential improvement in pain and risk of reoperation, especially in a young woman (33). Medical management of menopausal symptoms with hormone therapy after BSO carries the risk of recurrence of endometriosis and associated pain and should be used with caution (50). Unopposed E may be more likely to promote growth of endometriosis and disease recurrence than combined E-progestogen regimens, but no studies have compared the two treatments directly. In 1 randomized trial involving 172 women treated by hysterectomy and BSO for endometriosis, the incidence of recurrent disease after a mean 46 months of follow-up in those who subsequently received cyclic E and progestogen therapy was relatively low (3.5%) compared with untreated controls (0) (51). Continuous combined E-progestogen therapy is the commonly recommended regimen for treating menopausal symptoms in

women with endometriosis, an exception to the usual recommendation for E-only treatment after hysterectomy.

MEDICAL THERAPIES FOR ENDOMETRIOSIS

Assessing the success of medical treatment for endometriosis is difficult. Few randomized, controlled trials have evaluated the individual medical options (52–55). Randomized trials comparing different agents are confounded by the side effects associated with the medications. In addition, placebo effects in the range of 40%–45% have been reported in studies monitoring the subjective end point of pain (56).

Oral contraceptives (OC), progestogens, danazol, GnRH-a, and anti-progestogens all have been used for the treatment of endometriosis (57). Clinical trials involving such treatments are difficult because they routinely result in amenorrhea, and some result in hypoestrogenic effects that interfere with efforts to perform a blinded study. No studies have compared directly medical versus surgical treatment of endometriosis, and thus there is no substantial evidence to establish the superiority of one approach than the other. Costs and side effects often dictate the choice of medical treatment.

Nonsteroidal Anti-Inflammatory Drugs

First-line medical treatment for pain due to endometriosis is often a nonsteroidal anti-inflammatory drug, either by prescription or over-the-counter. Although these antiprostaglandin agents have been shown to be effective for the treatment of primary dysmenorrhea (58), a Cochrane analysis found insufficient data to show that they significantly reduce endometriosis pain (59).

Combined Hormonal Contraceptives

Combined hormonal contraceptives have been used in both a cyclic and a continuous fashion in the treatment of symptoms associated with endometriosis. Decidualization followed by atrophy of the endometrial tissue is the proposed mechanism of action (60). Whereas combined OCs containing the more androgenic progestogens (19-nortestosterone derivatives) traditionally have been used to treat endometriosis symptoms, combined OCs containing the new generation progestogen, desogestrel, also have proven effective (61). A low-dose combined OC administered in a cyclic regimen to women with endometriosis was found as effective as GnRH-a treatment for relief of dyspareunia and nonmenstrual pain as assessed by a pain scoring system (62). However, GnRH-a treatment was more effective than combined OCs for the relief of dysmenorrhea because the agonist reliably induces amenorrhea (62). A prospective observational trial demonstrated that continuous low-dose combined OCs were more effective than cyclic combined OCs in controlling endometriosis symptoms in patients after surgical treatment for endometriosis (63).

Progestogens

Progestogens most commonly used for the treatment of endometriosis include medroxyprogesterone acetate (MPA) and 19-nortestosterone derivatives (e.g., levonorgestrel, norethindrone acetate, and dienogest). As with OCs, their proposed mechanism of action involves decidualization and subsequent atrophy of endometrial tissue. Another more recently proposed mechanism involves progestogen-induced suppression of matrix metalloproteinases, a class of enzymes important in the growth and implantation of ectopic endometrium (60). Inhibition of angiogenesis has also been proposed as a mechanism to explain the effectiveness of progestins in the treatment of endometriosis (64). In observational studies involving treatment with MPA, dydrogesterone, or norethindrone acetate, pain has been reduced by 70%–100% (65). A meta-analysis of four randomized, controlled trials comparing MPA to danazol alone, danazol and combined OCs, or a GnRH-a (goserelin acetate) concluded that MPA was as effective as the other treatments (odds ratio [OR] 1.1; 95% CI 0.4–3.1) (65). Randomized studies concluded that dienogest was significantly better than placebo and as effective as the GnRH-a buserelin, LA, or triptorelin in reducing pain symptoms with diminished side effects of hot flushes and bone mineral density loss (66).

The levonorgestrel-releasing intrauterine system (LNG-IUS) represents another approach to the medical treatment of endometriosis. A randomized, controlled trial comparing the LNG-IUS to expectant management after laparoscopic surgical treatment for symptomatic endometriosis found that the LNG-IUS was more effective than no treatment in reducing symptoms of dysmenorrhea (67). Other studies have demonstrated improved symptoms associated with rectovaginal endometriosis (68) and a significant decrease in the extent of disease observed at second-look laparoscopy after 6 months of treatment with the LNG-IUS (69). Relief of endometriosis pain with the LNG-IUS is similar to GnRH-a (52, 70).

Danazol

Danazol is a derivative of 17 α-ethinyltestosterone and acts primarily by inhibiting the LH surge and steroidogenesis and by increasing free T levels (60). Hyperandrogenic side effects are common and include hirsutism, acne, weight gain, and deepening of the voice (55). Typically this medication is administered orally; however, vaginal administration as well as vaginal and intrauterine delivery systems have been reported (71–74). When compared with placebo, danazol treatment was effective in relieving painful symptoms due to endometriosis, and laparoscopic scores improved. Danazol provided comparable pain relief to GnRH-a but was not as well tolerated (52).

GnRH Agonists

Gonadotropin-releasing hormone agonist treatment for endometriosis has been studied more extensively than other medical treatment regimens. Gonadotropin-releasing hormone agonists are modified forms of GnRH that bind to receptors in the pituitary but have a longer half-life than native GnRH and thereby result in down-regulation of the pituitary-ovarian axis and hypoestrogenism. The likely mechanism of action for relief of endometriosis pain involves the induction of amenorrhea and progressive endometrial

atrophy (60). Gonadotropin-releasing hormone agonists can be administered by a calibrated nasal spray twice daily (nafarelin acetate), by injection of either a short-acting formulation daily, or by injection of a depot formulation (LA, goserelin acetate) every 1–3 months. Side effects relate primarily to the induced hypoestrogenic state and include hot flushes, vaginal dryness, decreased libido, mood swings, headache, and bone mineral depletion (75). A Cochrane analysis found that GnRH-a were more effective than placebo for endometriosis pain relief but were similar to the LNG-IUS and danazol (52). A long-term follow-up study of patients treated with a GnRH-a alone for 6 months revealed a 53% recurrence of disease/symptoms 2 years after treatment (28).

To reduce negative effects of E deprivation (e.g., bone loss, hot flushes) and allow for longer treatment periods, "add-back" therapy with norethindrone acetate or a combination of E and progestogen has been advocated. This treatment regimen decreases bone loss seen with GnRH-a alone and also reduces the severity of hypoestrogenic side effects associated with GnRH-a treatment. The underlying theory of add-back treatment is the "E threshold hypothesis," which holds that the amount of E and/or progestogen necessary to prevent hot flushes, bone loss, and other hypoestrogenic symptoms and side effects is less than that which would stimulate endometriosis (76). Although norethindrone acetate is the only hormone approved by the US Food and Drug Administration for add-back therapy, other combinations of low-dose E and progestogens also have been shown to be effective in decreasing hypoestrogenic side effects and maintaining bone density, and not adversely affecting the extent of pain relief achieved with GnRH-a treatment (52, 77). The add-back therapy should be started at the same time as the agonist rather than delaying until a period of hypoestrogenism has occurred. This approach has been shown to decrease bone loss and improve vasomotor symptoms and compliance (78).

Gestrinone

Gestrinone (ethylnorgestrienone, R2323) is an antiprogestational steroid used in Europe for the treatment of endometriosis, but it is not currently available in the United States (53). The mechanism of action includes a progestational withdrawal effect at the endometrial cellular level and inhibition of ovarian steroidogenesis (60). The drug is administered orally daily to weekly with doses ranging from 2.5–10 mg. Side effects relate to both androgenic and antiestrogenic effects. Gestrinone was shown to be as effective as danazol and GnRH analogues (54).

Aromatase Inhibitors

In several studies involving small numbers of patients, aromatase inhibitors have been shown to be effective for the treatment of endometriosis and pelvic pain in premenopausal and postmenopausal women (79, 80). However, such treatment still is considered investigational, is not approved by the US Food and Drug Administration for this indication, and should not be considered as definitive therapy. Endometriotic tissue, unlike disease-free endometrium, ex-

hibits a high level of aromatase activity that may result in increased local concentrations of E that may favor growth of endometriosis (20, 79). This observation may help to explain the presence of endometriosis in postmenopausal women and the persistence of disease symptoms in some patients receiving GnRH-a treatment. A randomized trial of women on goserelin treated with anastrozole or placebo reported no difference in symptom scores during treatment, but the anastrozole group had a lower recurrence rate as well as a longer time to symptom recurrence (81). However, anastrozole increased bone loss compared with goserelin alone (81). In premenopausal women aromatase inhibitors lead to an increase in FSH levels and subsequent follicular development and therefore must be used in combination with additional agents (progestogens, combined OCs, or GnRH-a) to down-regulate the ovaries. The combination of an aromatase inhibitor with a combined OC may improve endometriosis pain while suppressing follicle development and preserving bone mineral density (79).

Other Medical Treatments Under Investigation

Medical treatment options for endometriosis currently under investigation include RU486 (mifepristone), selective PR modulators, selective ER modulators, GnRH antagonists, pentoxifylline, and agents that inhibit the effect of tumor necrosis factor (TNF)-α, matrix metalloproteinases, and angiogenesis (60).

Ancillary Treatments

Chronic pelvic pain from endometriosis may cause postural changes and muscle contractures leading to musculoskeletal pain (82). Referral to a physiotherapist trained in pelvic floor rehabilitation can be very beneficial in relieving that component of the pain. In addition, referral to a mental health professional should be considered to address the psychological stress and depression that may be associated with chronic pelvic pain. It can also be helpful to involve a pain management specialist to coordinate analgesic treatment as well as to provide other modalities such as neuroleptic drugs and nerve blocks.

Acupuncture can also be considered an adjunctive therapy for pelvic pain associated with endometriosis. Two randomized studies evaluated specific versus sham acupuncture for endometriosis pain and both reported significantly better pain relief with true acupuncture (83, 84). Finally, randomized clinical trials comparing Chinese herbal medicine treatment to gestrinone and danazol concluded that Chinese herbal medicine had comparable results with fewer side effects (85).

MEDICAL THERAPY AFTER CONSERVATIVE SURGERY FOR ENDOMETRIOSIS

Several studies have investigated the value of postoperative medical therapy. One prospective study found that, compared with placebo, 6 months of treatment with a GnRH-a (nafarelin acetate) after laparoscopic surgery for endometriosis resulted in greater improvement in pelvic pain and a longer interval before further treatment was required (86). A small randomized trial comparing a 3-month course of triptorelin or placebo found no difference by 5 years in recurrence of pain or

endometriomas (87). In a larger study involving 269 women treated for 6 months with a GnRH-a (goserelin acetate) after aggressive surgical resection, postoperative medical treatment significantly delayed the time to symptom recurrence when compared with expectant management (88). A randomized trial compared 6 months of goserelin to low-dose combined OCs and found comparable pain relief and symptom recurrence at 1 year (63).

Another study randomized women on postoperative GnRH-a therapy to the aromatase inhibitor, anastrozole, or placebo. The anastrozole group had decreased symptom recurrence and a longer pain-free interval after treatment (82). In a small randomized, controlled trial, treatment with danazol or MPA for 6 months after laparoscopy resulted in significantly more pain relief and reduction in the size of endometriotic lesions than placebo at the time of second-look laparoscopy (89). Oral contraceptives decreased dysmenorrhea while on treatment as well as anatomic relapse of endometriosis. The benefit was lost upon discontinuation of treatment (90). Postoperative combined OC use did not reduce the recurrence of dyspareunia or chronic pelvic pain (91). A nonrandomized study reported a 36-month cumulative endometrioma recurrence rate after cystectomy of 6% with combined OCs versus 49% with no treatment (92). There are conflicting results regarding the effectiveness of continuous versus cyclic regimens for limiting the recurrence of pain and endometriomas (90–93).

LONG-TERM MANAGEMENT

Endometriosis potentially is a chronic disease that can result in significant morbidity. Consequently, a long-term management plan is beneficial. Endometriosis is best viewed primarily as a medical disease with surgical back-up. Individuals with chronic superficial or presumed disease should be treated medically, reserving surgery for those having large endometriomas or palpable disease that fails to respond to treatment. For women diagnosed with endometriosis in the past, and those with recurrent symptoms, medical management again is the preferred approach. In such women, and in those who fail to respond to medical therapy, other causes of pelvic pain should be considered carefully before attributing the symptoms to endometriosis. Multiple surgical procedures should be avoided whenever possible, because surgery has inherent risks and also might result in adhesions that can cause pelvic pain and decreased ovarian reserve. Women of reproductive age with endometriosis should be encouraged to pursue pregnancy at the earliest time that life circumstances allow because their disease has the potential to threaten their fertility.

SUMMARY

- Gastrointestinal, urinary, musculoskeletal, and psychological conditions can mimic the symptoms of endometriosis and should be excluded before pursuing aggressive therapy for endometriosis in all patients, particularly those who fail to respond to standard medical treatments.

- Theories to explain the pain associated with endometriosis include the actions of humoral factors, the effects of active bleeding from implants, and the irritation or invasion of pelvic floor nerves by infiltrating implants.
- Laparoscopy remains the cornerstone of accurate diagnosis of endometriosis.
- Both medical and surgical treatments for pain associated with endometriosis are effective.
- In women with symptoms of pelvic pain, visible endometriosis observed during surgery should be treated.
- The optimal surgical technique for treating endometriosis and/or endometriomas has not been established, although excision of the endometrioma cyst wall lowers the risk of recurrence compared with fenestration and ablation of the cyst wall.
- Surgical treatment for endometriosis, followed by medical therapy, offers longer symptom relief than surgery alone.

CONCLUSIONS

- Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.
- Definitive treatment of endometriosis with hysterectomy and BSO should be reserved for women with debilitating symptoms that can reasonably be attributed to the disease. These women should have completed childbearing and have failed to respond to alternative treatments.
- Further studies designed to compare medical and surgical treatments are clearly warranted.

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REFERENCES

1. Spaczynski RZ, Duleba AJ. Diagnosis of endometriosis. Semin Reprod Med 2003;21:193–208.

2. Gruppo Italiano per lo Studio dell'Endometriosi. Relationship between stage, site and morphological characteristics of pelvic endometriosis and pain. Hum Reprod 2001;16:2668–71.

3. Ballard KD, Seaman HE, de Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case–control study-Part 1. BJOG 2008;115:1382–91.

4. ACOG Committee on Practice Bulletins–Gynecology. ACOG Practice Bulletin No. 51: Chronic pelvic pain. Obstet Gynecol 2004;103:589–605.

5. Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain: relation to disease stage and localization. Fertil Steril 1996;65:299–304.

6. Sutton CJ, Pooley AS, Ewen SP, Haines P. Follow-up report on a randomized controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal to moderate endometriosis. Fertil Steril 1997;68:1070–4.

7. Riley JL, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. Pain 1999;81:225–35.

8. Howard FM. Endometriosis and mechanisms of pelvic pain. J Min Invas Gynecol 2009;16:540–50.

9. Porpora MG, Koninckx PR, Piazze J, Natili M, Colagrande S, Cosmi EV. Correlation between endometriosis and pelvic pain. J Am Assoc Gynecol Laparosc 1999;6:429–34.

10. Donnez J, Gillet N, Nisolle M, Beguin S, Smoes P, Casanas-Roux F. Peritoneal endometriosis and ''endometriotic'' nodules of the rectovaginal septum are two different entities. Fertil Steril 1996;66:362–8.

11. Anaf V, Simon P, El Nakadi I, Fayt I, Buxant F, Simonart T, et al. Relationship between endometriotic foci and nerves in rectovaginal endometriotic nodules. Hum Reprod 2000;15:1744–50.

12. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, editors. Handbook of pain assessment. New York: Guilford Press; 1992:135.

13. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277.

14. Fabbri E, Villa G, Mabrouk M, Guerrini M, Montanari G, Paradisi R, et al. McGill Pain Questionnaire: a multi-dimensional verbal scale assessing postoperative changes in pain symptoms associated with severe endometriosis. J Obstet Gynaecol Res 2008;35:753–60.

15. Biberoglu KO, Behrman SJ. Dosage aspects of danazol therapy in endometriosis: short-term and long-term effectiveness. Am J Obstet Gynecol 1981; 139:645–54.

16. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and the quality of life: correlations and predictive value of the SF-36. Pain Med 2003;4:331–9.

17. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? Br J Obstet Gynaecol 1998;105:1322–5.

18. Heitkemper MM, Cain KC, Jarrett ME, Burr RL, Hertig V, Bond EF. Symptoms across the menstrual cycle in women with irritable bowel syndrome. Am J Gastroenterol 2003;98:420–30.

19. Kubli-Garfias C. Modulatory action of 5-reduced androgens and progestogens on the excitability of CNS and smooth muscle. J Steroid Biochem 1987;27:631–4.

20. Bulun SE, Fang Z, Imir G, Gurates B, Tamura M, Yilmaz B, et al. Aromatase and endometriosis. Semin Reprod Med 2004;22:45–50.

21. Takayama K, Zeitoun K, Gunby RT, Sasano H, Carr BR, Bulun SE. Treatment of severe postmenopausal endometriosis with an aromatase inhibitor. Fertil Steril 1998;69:709–13.

22. Jansen RP, Russell P. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. Am J Obstet Gynecol 1986;155:1154–9.

23. Walter AJ, Hentz JG, Magtibay PM, Cornella JL, Magrina JF. Endometriosis: correlation between histologic and visual findings at laparoscopy. Am J Obstet Gynecol 2001;184:1407–13.

24. Balasch J, Creus M, Fabregues F, Carmona F, Ordi J, Martinez-Roman S, et al. Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study. Hum Reprod 1996;11:387–91.

25. Murphy AA, Green WR, Bobbie D, dela Cruz ZC, Rock JA. Unsuspected endometriosis documented by scanning electron microscopy in visually normal peritoneum. Fertil Steril 1986;46:522–4.

26. Nisolle M, Paindaveine B, Bourdon A, Berliere M, Casanas-Roux F, Donnez J. Histologic study of peritoneal endometriosis in infertile women. Fertil Steril 1990;53:984–8.

27. Ling FW, Pelvic Pain Study Group. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. Obstet Gynecol 1999;93:51–8.

28. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993;59: 511–5.

29. Dlugi AM, Miller JD, Knittle J, Lupron Study Group. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-blind study. Fertil Steril 1990;54:419–27.

30. Jacobson TZ, Duffy JMN, Barlow D, Koninckx PR, Garry R. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2009;4:CD001300.

31. Sutton CJ, Ewen SP, Whitelaw N, Haines P. Prospective randomized, double-blind controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. Fertil Steril 1994; 62:696–700.

32. Berlanda N, Vercellini P, Fedele L. The outcomes of repeat surgery for recurrent symptomatic endometriosis. Curr Opin Obstet Gynecol 2010;22: 320–5.

33. Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis. A 7-year follow-up on the requirement for further surgery. Obstet Gynecol 2008;111:1285–92.

34. Healey M, Ang WC, Cheng C. Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation. Fertil Steril 2010;94:2536.

35. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. Hum Reprod Update 2002;8:591–7.

36. Saleh A, Tulandi T. Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. Fertil Steril 1999;72: 322–4.

37. Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil Steril 1998;70:1176–80.

38. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochran Database Syst Rev 2008;2: CD004992.

39. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:3146–54.

40. Vercellini P, Vendola N, Bocciolone L, Colombo A, Rognoni MT, Bolis G. Laparoscopic aspiration of ovarian endometriomas: effect with postoperative gonadotropin releasing hormone agonist treatment. J Reprod Med 1992;37:577–80.

41. Donnez J, Nisolle M, Gillerot S, Anaf V, Clerckx-Braun F, Casanas-Roux F. Ovarian endometrial cysts: the role of gonadotropin-releasing hormone agonist and/or drainage. Fertil Steril 1994;62:63–6.

42. Marana R, Caruana P, Muzii L, Catalano GF, Mancuso S. Operative laparoscopy for ovarian cysts: excision vs. aspiration. J Reprod Med 1996;41:435–8.

43. Lichten EM, Bombard J. Surgical treatment of primary dysmenorrhea with laparoscopic uterine nerve ablation. J Reprod Med 1987;32:37–41.

44. Sutton C, Pooley AS, Jones KD, Dover RW, Haines P. A prospective randomized, double-blind controlled trial of laparoscopic uterine nerve ablation in the treatment of pelvic pain associated with endometriosis. Gynecol Endosc 2001;10:217–22.

45. Vercellini P, Aimi G, Busacca M, Apolone G, Uglietti A, Crosignani PG. Laparoscopic uterosacral ligament resection for dysmenorrhea associated with endometriosis: results of a randomized, controlled trial. Fertil Steril 2003; 80:310–9.

46. Davis GD. Uterine prolapse after laparoscopic uterosacral transection in nulliparous airborne trainees: a report of three cases. J Reprod Med 1996; 41:279–82.

47. Candiani GB, Fedele L, Vercellini P, Bianchi S, di Nola G. Presacral neurectomy for the treatment of pelvic pain associated with endometriosis: a controlled study. Am J Obstet Gynecol 1992;167:100–3.

48. Zullo F, Palomba S, Zupi E, Russo T, Morelli M, Cappiello F, et al. Effectiveness of presacral neurectomy in women with severe dysmenorrhea caused by endometriosis who were treated with laparoscopic conservative surgery: a 1-year prospective randomized double-blind controlled trial. Am J Obstet Gynecol 2003;189:5–10.

49. Namnoum AB, Hickman TN, Goodman SB, Gehlbach DL, Rock JA. Incidence of symptom recurrence after hysterectomy for endometriosis. Fertil Steril 1995;64:898–902.

50. Hickman TN, Namnoum AB, Hinton EL, Zacur HA, Rock JA. Timing of estrogen replacement therapy following hysterectomy with oophorectomy for endometriosis. Obstet Gynecol 1998;9:673–7.

51. Matorras R, Elorriaga MA, Pijoan JI, Ramon O, Rodriguez–Esscudero FJ. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. Fertil Steril 2002;77:303–8.

52. Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev 2010; 12:CD008475.

53. Davis L, Kennedy SS, Moore J, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev 2007;3:CD001019.

54. Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev 2012;3: CD002122.

55. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2001;4:CD000068.

56. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. JAMA 1994;271:1609–14.

57. Gambone JC, Mittman BS, Munro MG, Scialli AR, Winkel CA, Chronic Pelvic Pain/Endometriosis Working Group. Consensus statement for the management of chronic pelvic pain and endometriosis: proceedings of an expert-panel consensus process. Fertil Steril 2002;78:961–72.

58. Marjoribanks J, Proctor ML, Farquhar C. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. Cochrane Database Syst Rev 2003;4: CD001751.

59. Allen C, Hopewell S, Prentice A, Gregory D. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev 2009;2:CD004753.

60. Olive DL. Medical therapy of endometriosis. Semin Reprod Med 2003;21: 209–22.

61. Razzi S, Luisi S, Ferretti C, Calonaci F, Gabbanini M, Mazzini M, et al. Use of a progestogen-only preparation containing desogestrel in the treatment of recurrent pelvic pain after conservative surgery for endometriosis. Eur J Obstet Gynecol Reprod Biol 2007;135:188–90.

62. Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60: 75–9.

63. Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril 2003;80:560–3.

64. Laschke MW, Menger MD. Anti-angiogenic treatment strategies for the therapy of endometriosis. Hum Reprod Update 2012;18:682–702.

65. Vercellini P, Cortesi I, Crosignani PG. Progestogens for symptomatic endometriosis: a critical analysis of the evidence. Fertil Steril 1997;68: 393–401.

66. McCormack PL. Dienogest. A review of its use in the treatment of endometriosis. Drugs 2010;70:2073–88.

67. Vercellini P, Frontino G, de Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril 2003;80:305–9.

68. Fedele L, Bianchi S, Zanconato G, Portuese A, Raffaelli R. Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. Fertile Steril 2001;75:485–8.

69. Lockhat FB, Emembolu JO, Konje JC. The evaluation of the effectiveness of an intrauterine-administered progestogen (levonorgestrel) in the symptomatic treatment of endometriosis and in the staging of the disease. Hum Reprod 2004;19:179–84.

70. BayogluTekin Y, Dilbaz B, Altinbas SK, Dilbaz S. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril 2011;95:492–6.

71. Ferrero S, Tramalloni D, Venturini PL, Remorgida V. Vaginal danazol for women with rectovaginal endometriosis and pain sympotms persisting after insertion of a levonorgestrol-releasing intrauterine device. Int J Gynecol Obstet 2011;113:116–9.

72. Mizutani T, Nishiyama S, Amakawa I, Watanabe A, Nakamuro K, Terada N. Danazol concentrations in ovary, uterus, and serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. Fertil Steril 1995;63:1184–9.

73. Igarashi M, Iizuka M, Abe Y, Ibuki Y. Novel vaginal danazol ring therapy for pelvic endometriosis, in particular deeply infiltrating endometriosis. Hum Reprod 1998;13:1952–6.

74. Cobellis L, Razzi S, Fava A, Severi FM, Igarashi M, Petraglia F. A danazol-loaded intrauterine device decreases dysmenorrhea, pelvic pain, and dyspareunia associated with endometriosis. Fertil Steril 2004;82:239–40.

75. Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Cochrane Database Syst Rev 2003;4:CD001297.

76. Barbieri RL. Endometriosis and the estrogen threshold theory: relation to surgical and medical treatment. J Reprod Med 1998;43:287–92.

77. Hornstein MD, Surrey ES, Weisberg GW, Casino LA, Lupron Add-Back Study Group. Leuprolide acetate-depot and hormonal add-back in endometriosis: a 12-month study. Obstet Gynecol 1998;91:16–24.

78. Kiesl L, Schweppe K-W, Sillam M, Siebzehnrübl E. Should add-back therapy for endometriosis be deferred for optimal results? Br J Obstet Gynaecol 1996;103(Suppl 14):15–7.

79. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis. Fertil Steril 2012;98:1370–9.

80. Nawathe A, Patwardhan S, Yates D, Harrison GR, Khan KS. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. Br J Obstet Gynaecol 2008;115:818–22.

81. Soysal S, Soysal ME, Ozer S, Gul N, Gezgin T. The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial. Hum Reprod 2004;19:160–7.

82. Montenegro ML, Vasoncelos EC, Candido dos Reis FJ, Nogueira AA, Poli-Neto OB. Physical therapy in the management of women with chronic pelvic pain. Int J Clin Pract 2008;62:263–9.

83. Wayne PM, Kerr CE, Schnyer RN, Legedza AT, Savetsky-German J, Shields MH, et al. Japanese-style acupuncture for endometriosis-related pelvic pain in adolescents and young women: results of a randomized sham-controlled trial. J Pediatric & Adolescent Gynecol 2008;21:247–57.

84. Rubi-Klein K, Kucera-Sliutz E, Nissel H, Bijak M, Stockenhuber D, Fink M, et al. Is acupuncture in addition to conventional medicine effective as pain treatment for endometriosis? A randomised controlled cross-over trial. Eur J Obstet Gynecol Reprod Biol 2010;153:90–3.

85. Flower A, Liu JP, Lewith G, Little P, Li Q. Chinese herbal medicine for endometriosis. Cochrane Database Syst Rev 2012;5:CD006568.

86. Hornstein MD, Hemmings R, Yuzpe AA, Heinrichs WL. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. Fertil Steril 1997;68:860–4.

87. Loverro G, Carriero C, Rossi AC, Putignano G, Nicolardi V, Selvaggi L. A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III–IV endometriosis. Eur J Obstet Gynecol Reprod Biol 2008;136:194–8.

88. Vercellini P, Crosignani PG, Fadini R, Radici E, Belloni C, Sismondi P. A gonadotrophin-releasing hormone agonist compared with expectant management after conservative surgery for symptomatic endometriosis. Br J Obstet Gynaecol 1999;106:672–7.

89. Telimaa S, Ronnberg L, Kauppila A. Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis after conservative surgery. Gynecol Endocrinol 1987;1:363–71.

90. Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frasca C, Elmakky A, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. Hum Reprod 2009;24:2729–35.

91. Seracchioli R, Mabrouk M, Frasca C, Manuzzi L, Savelli L, Venturoli S. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. Fertil Steril 2010;94:464–71.

92. Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. Am J Obstet Gynecol 2008;198:504.e1–5.

93. Muzii L, Maneschi F, Marana R, Porpora MG, Zupi E, Bellati F, et al. Oral estroprogestins after laparoscopic surgery to excise endometriomas: continuous or cyclic administration? Results of a multicenter randomized study. J Min Invas Gynecol 2011;18:173–8.