Treatment of pelvic pain associated with endometriosis

The Practice Committee of the American Society for Reproductive Medicine

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Pain associated with endometriosis requires careful evaluation to exclude other potential causes and may involve a number of different mechanisms. Both medical and surgical treatments for pain related to endometriosis are effective and choice of treatment must be individualized. (Fertil Steril® 2008;90:S260–9. ©2008 by American Society for Reproductive Medicine.)

Endometriosis is one of the most common gynecologic disorders and is found in approximately 70% of patients with chronic pelvic pain (1, 2). The evaluation and measurement 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 of pain production from endometriosis; 3) difficulty in determining the comparative success of medical and surgical therapies compared to placebo; and 4) the tendency for chronic pain to progressively involve additional surrounding organ systems beyond the reproductive tract. This document addresses the mechanisms by which endometriosis causes 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 a gynecologic condition. 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 non-gynecologic causes of pelvic pain may include irritable bowel syndrome (IBS), interstitial cystitis, fibromyalgia, and musculoskeletal disorders such as trigger point pain and pelvic floor dysfunction (3). It may be difficult to distinguish endometriosis from these conditions since 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 prior to aggressive therapy for endometriosis and also in those women who do not respond to conventional therapy for endometriosis.

MECHANISMS OF PAIN IN ENDOMETRIOSIS

Endometriosis can appear in a variety of 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 via different mechanisms. While 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 (4). Although considered a progressive disease, endometriosis also can remain static and even regress without treatment (5).

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 (6); 2) the direct and indirect effects of active bleeding from endometriotic implants; and 3) irritation or direct invasion of pelvic floor nerves or direct invasion of those nerves by infiltrating endometriotic implants, especially in the cul-de-sac (7). It remains plausible, of course, 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 over 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 (8). 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 (7).

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 or more below the peritoneal surface (8). Both perineural inflammation and direct infiltration of nerves by endometriosis have been observed (9). However, this kind of perineural change has 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 that

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are not used in clinical practice such as a Visual Analog Scale (rating pain from "none" to "worst ever" (10)), the McGill Pain Questionnaire (11), or a unique simple categorical scale (12). Quality of life scales, such as the SF-36, also are used to assess the impact of pain and the response to treatment (13).

Impact of the Gonadal Steroids on Pain

Estrogen 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 about 30% in the immediately premenstrual and menstrual phases of the cycle when estrogen levels are low (6). This observation is consistent with the well-documented phenomenon of increased symptoms of IBS immediately before and during menses, even though bowel motility does not seem to change measurably in women with IBS during these time periods. 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 (14).

Estrogen increases pain associated with endometriosis by directly stimulating growth of the lesions. Endometriotic lesions demonstrate variable levels of estrogen and progesterone receptors and hormonal responsiveness (8). 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 (15). This observation may help explain persistent or recurrent disease in estrogen-deficient states (16).

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 (4, 17). Pelvic examination is notoriously inaccurate in estimating the volume of endometriosis, and X-ray, ultrasound, and 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 (18). Atypical lesions, including those within peritoneal pockets, are more difficult to characterize without biopsy (19, 20). Although studies suggest that microscopic endometriosis may routinely elude detection with laparoscopy (21, 22), it is believed that these forms of the disease may play a lesser, if any, role in the pain associated with endometriosis (20). Once endometriosis has been diagnosed, progression of the disease is not reliably assessed by pain symptoms or radiologic tests.

Gonadotropin-releasing hormone (GnRH) agonists have been advocated to diagnose and treat endometriosis without performing laparoscopy, based primarily on the results of one study involving 95 women with moderate to severe chronic pelvic pain unrelated to menstruation who were randomized to receive depo-leuprolide 3.75 mg or placebo injection monthly for three months followed by laparoscopy (23). The underlying premise was that improved pain symptoms during the hypoestrogenic state induced by GnRH agonist treatment might reliably indicate that endometriosis was the cause (24, 25). However, pain relief in response to depo-leuprolide 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 depo-leuprolide did not accurately diagnose the disease. Treatment with leuprolide for three months did improve dysmenorrhea, pelvic pain, and dyspareunia, regardless of the presence of endometriosis. Establishing the correct diagnosis by laparoscopy prior to initiating therapy with medication that is associated with significant short- and long-term side effects is the preferred approach, although further studies are warranted.

SURGICAL THERAPY FOR ENDOMETRIOSIS

Relief of pain following surgical treatment of endometriosis at one-year follow-up ranges between 50% and 95% (Table 1) (26–35). A randomized controlled study evaluating laparoscopic laser treatment of minimal to moderate disease observed no difference in the proportion of patients reporting improved pain three months following laser treatment or diagnostic laparoscopy without treatment (56% and 48%, respectively, $P=0.35$) (31). However, at six months after surgery, pain was significantly improved in 62.5% of those who received laser treatment and in only 22.6% of controls ($P<0.01$). The proportion of patients with improved pain symptoms was significantly higher among those with moderate and mild endometriosis (approximately 100% and 70%, respectively) than in women with minimal disease (approximately 40%) (31). A follow-up study one year after conservative laparoscopic treatment of endometriosis observed recurrent disease in 44% (5). Taken together, these observations indicate that laparoscopic treatment of visible endometriosis does lead to improvement in pain and, thus, support the recommendation to treat endometriotic lesions seen at the time of diagnostic laparoscopy.

Surgical options for the treatment of endometriosis include the use of unipolar or bipolar cautery, laser ablation using KTP, CO2, or neodymium: yittrium, aluminum, garnet (Nd:YAG) lasers, and excision techniques, but no randomized trials have evaluated their comparative efficacies. Each has advantages and disadvantages with respect to lesion removal, tissue trauma and bleeding.

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 (36). Conservative surgical options include excision of the cyst wall, drainage and

TABLE 1

Surgical therapy for endometriosis.

Author study design	N	F/u time	F/u N	Results
Wheeler & Malinak (26) case series	423	3 yrs. 5 yrs.	161 77	13.5% re-operation for pain 40.3% re-operation for pain
Davis (32) case series	158	15 mos.	158	5–7% recurrence of dysmenorrhea and dyspareunia
Sutton & Hill (29) case series	228	1–6 yrs.	181	30% recurrence of pain
Redwine (27) case series	359	2.03 yrs.	336	19.5% re-operation for pain over 5 yrs, by life-table analysis
Sutton et al. (31) randomized, double blind controlled	63	6 mos.	63	38.7% recurrence of pain in treated group vs 77.4% in controls
Donnez et al. (30) case series	500	6 mos, 2 yrs.	242	No recurrences at 6 mos. At 2 yrs, 1.2% recurrence of dysmenorrhea, 3.7% recurrence of dyspareunia (excision of infiltrated cul-de-sac disease)
Chapron et al. (28) case series	110	17 mos.	110	12% recurrence of pain

Note: F/u = follow-up; N = number.

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coagulation/ablation of the cyst, and simple drainage of the cyst. Cyst excision is more effective than fenestration and ablation of the cyst wall. A retrospective study involving 231 patients found that re-operation rates after 42 months of follow-up were lower after cyst excision than after fenestration and ablation (23.5% vs. 57.8%, respectively) (37). Cyst excision also achieves greater improvements in symptoms of dysmenorrhea, deep dyspareunia, and nonmenstrual pain, compared with fenestration and coagulation (38). Simple drainage of endometriomas is associated with a high risk of cyst recurrence (80% to 100%) within six months and, therefore, is not recommended as definitive therapy (39–41).

Laparoscopic Uterosacral Nerve Ablation

Laparoscopic uterosacral nerve ablation (LUNA) is a technique designed to disrupt the efferent nerve fibers in the uterosacral ligaments to decrease uterine pain for women with intractable dysmenorrhea (42, 43). However, a large randomized controlled trial comparing results of conservative laparoscopic surgery for endometriosis to conservative surgery with LUNA observed no difference between groups in the proportions of patients having recurrent dysmenorrhea one and three years following surgery (44). Currently, LUNA does not appear to offer any added benefits beyond those that can be achieved with conservative surgery alone. Although LUNA has a low risk of complications, uterine prolapse and transection of the ureter can and do occur (45).

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 time of conservative surgery for endometriosis decreased midline dysmenorrhea but did not improve other symptoms of dysmenorrhea, dyspareunia, or pelvic pain (46). Another randomized controlled trial involving 141 women that compared results achieved with conservative laparoscopic surgery for endometriosis, with and without presacral neurectomy, observed that women treated by presacral neurectomy experienced significantly greater improvements in symptoms of dysmenorrhea, dyspareunia, and pelvic pain six and 12 months after surgery, compared with women treated by conservative surgery alone (47). Presacral neurectomy has been proposed for 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.

Hysterectomy

Hysterectomy with bilateral salpingo-oophorectomy (TAH-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 of the disease and the resulting surgical menopause causing atrophy of endometrial tissue. Hysterectomy without bilateral salpingo-oophorectomy is less effective, as disease recurrence and subsequent re-operation rates are higher (48).

Medical management of menopausal symptoms with hormone replacement following bilateral salpingo-oophorectomy carries the risk of recurrence of endometriosis and associated pain, and should be used with caution (49). Unopposed estrogen may be more likely to promote growth of endometriosis and disease recurrence than combined estrogen-progestogen regimens, but no studies have compared the two treatments directly. In one randomized trial involving 172 women treated by TAH-BSO for endometriosis, the incidence of recurrent disease after a mean 46 months of follow-up in those who subsequently received cyclic estrogen and progestogen replacement was relatively low (3.5%), compared with untreated controls (0%) (50). Continuous combined estrogen-progestogen therapy is the recommended regimen for treating menopausal symptoms in women with endometriosis, an exception to the usual recommendation for estrogen only treatment after hysterectomy.

MEDICAL THERAPIES FOR ENDOMETRIOSIS

Oral contraceptives (OCs), progestogens, danazol, GnRH agonists, and anti-progestogens all have been employed for the treatment of endometriosis (Table 2) (51). 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 vs. surgical treatment of endometriosis and, thus, there is no substantial evidence to establish the superiority of one approach over the other. Costs and side effects often dictate the choice of medical treatment.

Combined Oral Contraceptives

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 (52). Whereas OCs containing the more androgenic progestogens (19-nortestosterone derivatives) traditionally have been used to treat endometriosis symptoms, combined contraceptives containing the new generation progestogen, desogestrel, also have proven effective (53).

Progestogens

Progestogens most commonly used for the treatment of endometriosis include medroxy-progesterone acetate and 19-nortestosterone derivatives (e.g., norethindrone acetate). As with oral contraceptives, their proposed mechanism of action involves decidualization and subsequent atrophy of endometrial tissue. Another, more recently proposed, mechanism involves a progestogen-induced suppression of matrix metalloproteinases, a class of enzymes important in the growth and implantation of ectopic endometrium (52).

The levonorgestrel-releasing intrauterine system (Lng-IUS) represents another novel approach to the medical treatment of endometriosis. The mechanism of action is unknown. 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 (54). Other studies have demonstrated improved symptoms associated with recto-vaginal endometriosis (55) and a significant decrease in the extent of disease observed at second-look laparoscopy after six months of treatment with the Lng-IUS (56). However, the device is not approved for this indication by the FDA.

Danazol

Danazol is a derivative of 17α-ethinyltestosterone and acts primarily by inhibiting the LH surge and steroidogenesis, and by increasing free testosterone levels (52). Common side effects relate to hyperandrogenism and include hirsutism, acne, and deepening of the voice. Alternate routes of danazol administration are under investigation (57–59).

GnRH Agonists

GnRH 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 involves the induction of amenorrhea and progressive endometrial atrophy (52). GnRH agonists can be administered via a calibrated nasal spray twice daily (nafarelin acetate), or by injection of either a short-acting formulation daily or of a depot formulation (leuprolide acetate) every one to three 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 (60). A long-term follow-up study of patients treated with a GnRH agonist alone for six months revealed a 53% recurrence of disease/symptoms two years after treatment (24).

"Add-back" therapy with a progestogen or a combination of estrogen and progestogen has been advocated for reducing the severity of hypoestrogenic side effects associated with GnRH agonist treatment. The underlying theory of add-back treatment is the "estrogen threshold hypothesis," which holds that the amount of estrogen 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 (61). Although norethindrone acetate is the only hormone approved by the FDA for add-back therapy, other combinations of conjugated estrogens and progestogens also have been shown effective for decreasing hypoestrogenic side effects and maintaining bone density,

TABLE 2

Medical therapy for endometriosis.

Author	Agents	N	Rx time	F/u time	Results
Oral contraceptives					
Vercellini et al. (69)	1. OCs 2. GnRHa	57	6 mos.	1 yr.	Equal impact on dysmenorrhea, dyspareunia, and daily pain
progestogens					
Telimaa et al. (80)	1. danazol, 600 mg qd 2. MPA 100 mg po qd 3. placebo	59	6 mos.	1 yr.	Both relieved pain equally
Telimaa et al. (77)	1. danazol 600 mg qd 2. MPA, 100 mg. po qd 3. placebo	60	6 mos.	1 yr.	(Following surgery) both relieved pain equally
Overton et al. (78)	1. dydrogesterone, 40 mg. qd, luteal 2. dydrogesterone 60 mg. qd, luteal 3. placebo	62	6 mos.	1 yr.	60 mg dose marginally better than placebo (90% vs. 75%) at 1 yr.
Vercellini et al. (79)	1. OCs & danazol 50 mg qd 2. MPA 150 mg IM q 3 mos.	80	1 yr.	1 yr.	MPA better at 1 yr.
progestogen IUD					
Fedele et al. (55)	1. Lng- IUD	11	12 mos.		Improved pain and decrease in size of rectovaginal lesion
Vercellini et al. (54)	1. Lng- IUD 2. expectant	40	12 mos.		Lng-IUD better at 1 yr.
Lockhat et al. (56)	1. levonorgestrel IUD	29	6 mos.		Improved pain with Lng-IUD at 6 mos.
Antiprogestogens					
Fedele et al. (81)	1. gestrinone, 2.5 mg 2–3/wk. 2. danazol 600–800 mg qd	39	6 mos.	1 yr.	Both relieved pain equally
Hornstein et al. (83)	1. gestrinone, 2.5 mg. 2×/wk 2. gestrinone, 1.25 mg. 2×/wk	12	6 mos.	6 mos.	Both relieved pain equally
Bromham et al. (82)	1. gestrinone, 2.5 mg, 2/wk 2. danazol, 400 mg qd	269	6 mos.	6 mos.	Both relieved pain equally
GISG (72)	1. gestrinone, 2.5 mg 2/wk 2. leuprorelin, 3.75 mg q mo.	55	6 mos.	6 mos.	Gestrinone relieved pain better
GnRH Agonists					
Wheeler et al. (84)	1. leuprolide acetate 3.75 mg q mo 2. danazol 800 mg daily	270	6 mos.		Both relieved pain, decreased disease equally
Rock et al. (85)	1. goserelin acetate, 3.6 mg q mo 2. danazol 800 mg daily	315	6 mos.		Both relieved pain, decreased ASRM score and lesion size equally

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TABLE 2

Continued.

Author	Agents	N	Rx time	F/u time	Results
Hornstein et al. (63)	Leuprolide acetate 3.75 mg q mo with: 1. placebo 2. norethindrone acetate 5 mg daily 3. norethindrone acetate 5 mg + conjugated equine estrogens 0.625 mg daily 4. norethindrone acetate 5 mg + conjugated equine estrogens 1.25 mg daily	201	12 mos.		Leuprolide acetate + norethindrone or norethindrone + conjugated equine estrogen 0.625 mg suppresses pain equally while protecting against bone loss.
Parazzini et al. (86)	1. ethinyl estradiol 0.03 mg + gestroden 0.75 mg daily 2. tryptorelin 3.75 mg q mo for 4 months, then ethinyl estradiol 0.03 mg + gestroden 0.75 mg daily for 8 mo	112	12 mos.		Both relieved pelvic pain equally at 12 mos.

Note: F/u = follow-up; N = Number.

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while not adversely affecting the extent of pain relief achieved with GnRH agonist treatment (62, 63).

Gestrinone

Gestrinone (ethylnorgestrienone, R2323) is an anti-progestational steroid used in Europe for the treatment of endometriosis, but it is not currently available in the United States (64). The mechanism of action includes a progestational withdrawal effect at the endometrial cellular level and inhibition of ovarian steroidogenesis (52). The drug is administered orally with doses ranging from 2.5 mg to 10 mg, administered daily to weekly. Side effects relate to both androgenic and antiestrogenic effects.

Aromatase Inhibitors

In pilot studies involving very small numbers of patients, aromatase inhibitors have been shown effective for the treatment of endometriosis and pelvic pain. However, such treatment still is considered investigational, is not approved by the FDA for this indication, and should not be considered as definitive therapy (16, 65). Endometriotic tissue, unlike disease-free endometrium, exhibits a high level of aromatase activity that may result in increased local concentrations of estrogen that may favor growth of endometriosis (15). At least in theory, that characteristic may help to explain observations of endometriosis in postmenopausal women and the persistence of disease symptoms in some patients receiving GnRH agonist treatment.

Other Treatments under Investigation

Medical treatment options for endometriosis currently under investigation include RU486 (mefipristone), selective progesterone receptor modulators, selective estrogen receptor modulators, GnRH antagonists, pentoxifylline, and agents that inhibit the effect of tumor necrosis factor (TNF)-α, matrix metalloproteinase, and angiogenesis (52).

Treatment Efficacy

Assessing the success of medical treatment for endometriosis is difficult. Few randomized, controlled trials have evaluated the individual medical options (62, 64, 66, 67). Randomized trials comparing different agents are confounded by the side effects associated with the medications. In addition, placebo effects in the range of 40% to 45% have been reported in studies monitoring the subjective end point of pain (68).

OCs administered in a cyclic or continuous fashion are effective in the treatment of endometriosis. A low-dose OC

administered in a cyclic regimen to women with endometriosis was found as effective as GnRH agonist treatment for relief of dyspareunia and non-menstrual pain as assessed by a pain scoring system (68). GnRH agonist treatment was more effective than OCs for the relief of dysmenorrhea because the agonist reliably induces amenorrhea (68). Continuous low-dose OCs (ethinyl estradiol 0.02 mg and desogestrel 0.15 mg) were compared with cyproterone acetate in a randomized trial that found no statistical difference between groups in the improvement in pain scores for dysmenorrhea, deep dyspareunia and non-menstrual pain (53). A subsequent prospective observational trial demonstrated that continuous low-dose OCs were more effective than cyclic OCs in controlling endometriosis symptoms in patients after surgical treatment for endometriosis (70).

Few studies have evaluated progestogens alone for the treatment of endometriosis (64). In observational studies involving treatment with medroxyprogesterone acetate (MPA), dydrogesterone, or norethindrone acetate, pain has been reduced by 70% to 100% (71). A meta-analysis of four randomized, controlled trials comparing MPA to danazol alone, danazol and OCs, or a GnRH agonist (goserelin acetate) concluded that MPA was as effective as the other treatments (OR 1.1; 95% CI, 0.4 to 3.1) (71).

GnRH agonist treatment for endometriosis has been studied more extensively than other medical treatment regimens. Among 26 studies that met the criteria for inclusion in the Cochrane database (62), 15 compared a GnRH agonist with danazol, and one study each compared a GnRH agonist with gestrinone, OCs, and a placebo. The remainder examined the results achieved with GnRH agonist treatment, with or without add-back therapy (five studies) or with various doses of GnRH agonists (three studies). Analysis of the 15 studies comparing various GnRH agonist treatment regimens with danazol, involving a total of 1,821 women, yielded no significant differences between the two drugs in pain relief or disease scores, regardless of the treatment (dose) regimen (62). Eight of these 15 studies examined American Society for Reprodutive Medicine (ASRM) disease scores after treatment, and only one (31) found that GnRH agonist was more effective than danazol in reducing the volume of disease (58.7% vs. 43.9%). In a single study that compared treatments with GnRH agonist and gestrinone, the progestogen was more effective in relieving symptoms of dysmenorrhea six months after cessation of therapy (72).

Numerous studies have compared the effectiveness of treatment with a GnRH agonist with and without add-back therapy (62, 73). The add-back regimens examined have included: MPA 100 mg daily, norethindrone 5 mg to 10 mg daily, estradiol 2 mg plus norethindrone 1 mg daily, and combined treatment with norethindrone acetate 5 mg and conjugated equine estrogen 0.625 mg or 1.25 mg daily. Add-back therapies did not alter the efficacy of GnRH agonist treatment, but did result in fewer side effects. Whereas add-back therapy maintained bone density in all treatment groups, bone density decreased in those treated with GnRH agonist alone and did not return to baseline levels at follow up. One trial in which OCs add-back therapy was employed observed fewer side effects, but no efficacy for the relief of pain (74).

MEDICAL THERAPY FOLLOWING CONSERVATIVE SURGERY FOR ENDOMETRIOSIS

Several studies have investigated the value of post-operative medical therapy. One prospective study found that, compared with placebo, six months of treatment with a GnRH agonist (nafarelin acetate) after laparoscopic surgery for endometriosis resulted in greater improvement in pelvic pain and a longer interval before further treatment was required (75). In a larger study involving 269 women treated for six months with a GnRH agonist (goserelin acetate) or placebo after aggressive surgical resection, postoperative medical treatment did not achieve significantly greater improvement in pain symptoms after one and two-years of follow-up, although there was a strong trend in that direction (76). In a small randomized, controlled trial, treatment with danazol or MPA for six months following laparoscopy resulted in significantly more pain relief and reduction in the size of endometriotic lesions than placebo at the time of second-look laparoscopy (77). No studies have evaluated post-operative therapy using less costly or intrusive treatments, such as cyclic or continuous OCs, or continuous progestogen treatment.

LONG-TERM MANAGEMENT

Endometriosis potentially is a chronic disease that can result in significant morbidity. Consequently, a long-term management plan would be beneficial. Endometriosis is viewed best 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 carefully considered 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. 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 AND CONCLUSIONS

- Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.

- 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 endometriosis are effective.
- In women with symptoms of pelvic pain, visible endometriosis observed during surgery should be treated.
- Surgical treatment for endometriosis, followed by medical therapy, offers longer symptom relief than surgery alone.
- Definitive treatment of endometriosis should be reserved for women with debilitating symptoms that can reasonably be attributed to the disease who 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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