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Management of Endometriosis

Endometriosis represents a significant health problem for women of reproductive age. The etiology, the relationship between the extent of disease and the degree of symptoms, the effect on fertility, and the most appropriate treatment of endometriosis remain incomplete. The purpose of this document is to present the evidence, including risks and benefits, for the effectiveness of medical and surgical therapy for adult women who are symptomatic with pelvic pain or infertility or both. Treatment options for adolescents are discussed in other documents (1).

Background

Incidence

Endometriosis is a gynecologic condition that occurs in 6–10% of women of reproductive age (2), with a prevalence of 38% (range, 20–50%) in infertile women (3–6), and in 71–87% of women with chronic pelvic pain (7–9). Contrary to much speculation, there are no data to support the view that the incidence of endometriosis is increasing (10), although improved recognition of endometriotic lesions may have led to an increase in the rate of detection (11). There also appears to be no particular racial predisposition to endometriosis.

A familial association of endometriosis has been suggested, and patients with an affected first-degree relative have nearly a 7–10-fold increased risk of developing endometriosis (12, 13). There is a strong concordance in monozygotic twins (14). The proposed inheritance is characteristic of a polygenic-multifactorial mechanism. A number of genetic polymorphisms have been identified (15).

Etiology

Endometriosis is a chronic gynecologic disorder whose principal manifestations are chronic pain and infertility. The pathogenesis of endometriosis is complex but is still thought to be principally associated with attachment and implantation of endometrial glands and stroma on the peritoneum from retrograde menstruation. Other theories such as hematogenous or lymphatic transport, stem cells from bone marrow, and coelomic metaplasia may explain some clinical circumstances (16).

The complex interaction between aberrant expression of endometrial genes as well as altered hormonal response will predispose patients to the development of endometrial lesions (17–20). Key components in the development of endometriosis are local overproduction of prostaglandins by an increase in cyclooxygenase-2 (COX-2) activity and overproduction of local estrogen by increased aromatase activity. Progesterone resistance dampens the antiestrogenic effect of progesterone and amplifies the local estrogenic effect (19).

The resulting endometrial lesions can lead to a chronic inflammatory disorder with increased numbers of activated macrophages and proinflammatory cytokines in the peritoneal fluid that may cause pain and infertility. The most commonly found inflammatory cytokines are tumor necrosis factor alpha and interleukins 1, 6, and 8 (21). These cytokines are associated with pain by several mechanisms, including the induction

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of prostaglandins. Nerve growth factor is also highly expressed in endometriotic lesions, especially in rectovaginal lesions (22). An increased density of nerve fibers in peritoneal endometriosis, especially deep infiltrating endometriosis, or close proximity of nerves to peritoneal lesions also can explain the common manifestation of pain (23–25). Changes in innervation of the uterus also have been reported in patients with endometriosis and may explain the severe dysmenorrhea and the improvement in symptoms from hysterectomy (26, 27).

Endometriosis is associated with infertility, although the mechanism by which this occurs with early stage disease is not clear (28). An abnormal peritoneal environment characterized by oxidative stress and higher concentrations of inflammatory cytokines may affect sperm function by a variety of mechanisms, including causing sperm DNA damage (29, 30). This abnormal peritoneal environment also can cause abnormalities in oocyte cytoskeleton function (30). Antimüllerian hormone, a marker of ovarian reserve, is decreased in early stage endometriosis (31). In more advanced endometriosis with ovarian cysts and adhesions, the anatomic abnormalities can result in abnormal tubal function.

Risk factors for developing endometriosis include early menarche (occurring before age 11 years), shorter cycles less than 27 days), and heavy, prolonged cycles (32, 33). Higher parity and increased duration of lactation were associated with a decreased risk of endometriosis among parous women (33). Regular exercise of more than 4 hours per week was associated with a reduced risk of developing endometriosis (34).

Clinical Manifestations

The clinical manifestations of endometriosis are variable and unpredictable in both presentation and course. Dysmenorrhea, chronic pelvic pain, dyspareunia, uterosacral ligament nodularity, and an adnexal mass (either symptomatic or asymptomatic) are among the well-recognized manifestations. A significant number of women with endometriosis remain asymptomatic. Endometriosis is more likely to be diagnosed in women with classic symptoms, including abdominopelvic pain (odds ratio [OR]=5.2), dysmenorrhea (OR=8.1), menorrhagia (OR=4.0), and dyspareunia (OR=6.0) than in controls (35).

Pelvic pain that is typical of endometriosis is characteristically described as secondary dysmenorrhea (with pain frequently commencing before the onset of menses), deep dyspareunia (exaggerated during menses), or sacral backache during menses. Endometriosis that involves specific organs may result in pain or physiologic dysfunction of those organs, such as perimenstrual tenesmus, diarrhea or constipation, cramping and dyschezia in cases of bowel involvement, or dysuria and hematuria in cases of bladder involvement (36, 37). Bladder or bowel symptoms may be present without lesions directly affecting the organ.

The pain associated with endometriosis may not correlate with the stage of disease but there may be some association with the depth of infiltration of endometriotic lesions (38, 39). Painful defecation during menses and severe dyspareunia are the most predictable symptoms of deeply infiltrating endometriosis (40).

Diagnosis

The definitive diagnosis of endometriosis only can be made by histology of lesions removed at surgery. Neither serum markers nor imaging studies have been able to supplant diagnostic laparoscopy for the diagnosis of endometriosis. The histologic appearance consists of endometrial glands and stroma with varying amounts of inflammation and fibrosis. However, the visual appearance of the lesions at laparoscopy is variable. Several studies have reported a marked discrepancy between the visual appearance and the histology (41–43). False-positive results occur because of the wide variety of lesions described as classical (black powder-burn lesions) or nonclassical (red or white lesions). Lesions may be missed without a careful inspection of the pelvis such as under the ovaries (ovarian fossa). Although biopsy is not always required at the time of laparoscopy, it should be performed if there is doubt as to the origin of the lesion. Cystoscopy with biopsy is recommended if there is suspicion of bladder endometriosis.

Imaging studies, such as ultrasonography, magnetic resonance imaging, and computed tomography appear to be useful only in the presence of a pelvic or adnexal mass (44). Ovarian endometriomas visualized with ultrasonography typically appear as cysts that contain low-level, homogeneous internal echoes consistent with old blood. Imaging studies alone appear to have high predictive accuracy in differentiating an ovarian endometrioma from other adnexal masses, and transvaginal ultrasonography is the imaging modality of choice when assessing the presence of endometriosis (45). Transvaginal ultrasonography is also the imaging technique of choice to detect the presence of deeply infiltrating endometriosis of the rectum or rectovaginal septum (46–49). Sometimes water contrast in the rectum may aid in the diagnosis of endometriosis infiltrating the bowel (50). Magnetic resonance imaging should be reserved for equivocal ultrasound results in cases of rectovaginal or bladder endometriosis (51, 52). The clinical utility of measuring CA 125 as a diagnostic marker for endometriosis is limited (53–56).

Classification

Numerous classification schemas have been proposed to describe endometriosis by anatomic location and severity of disease. The American Society for Reproductive Medicine (ASRM) classification, which is the most commonly used system, was revised for the third time in 1996 (see Fig. 1) but still has limitations (57). The system is not a good predictor of pregnancy after treatment despite adjustments to the point scores and cut-points for disease stage. The ASRM system does not correlate well with the symptoms of pain and dyspareunia or infertility. The value of the ASRM revised system is in uniform recording of operative findings and perhaps for comparing the results of various therapies.

Clinical Considerations and Recommendations

▶ ***In women with endometriosis-related infertility, what is the value of surgical therapy for endometriosis?***

Medical suppressive therapies such as oral contraceptives (OCs) or gonadotropin-releasing hormone (GnRH) agonists for endometriosis-associated infertility are ineffective according to a 2007 Cochrane review (58).

Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude of improvement is unclear. Two randomized controlled

American Society for Reproductive Medicine
Revised Classification of Endometriosis

Patient's name _____ Date _____

Stage I (minimal) — 1–5
Stage II (mild) — 6–15
Stage III (moderate) — 16–40
Stage IV (severe) — >40

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended treatment _____

Total _____

Prognosis _____

	Endometriosis	<1 cm	1–3 cm	>3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	Posterior cul-de-sac obliteration	Partial	Complete
		4	40

	Adhesions	<1/3 Enclosure	1/3–2/3 Enclosure	>2/3 Enclosure
Ovary	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16. Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B), black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___%, and B___%. Total should equal 100%.

Figure 1. Modified from the revised American Fertility Society classification of endometriosis. (Reprinted with permission from the American Society for Reproductive Medicine. Fertility and Sterility 1996;67(5):819–820.)

trials (RCT) investigated the effect of surgical treatment of stage I-II (minimal and mild) disease (59, 60) with contradictory results. A pooled analysis of these two trials shows an OR of 1.65 (95% confidence interval (CI), 1.06–2.58) for postsurgery conception, and a number needed to treat of 12 (61). The number of laparoscopies performed to obtain a pregnancy will depend on the prevalence of disease. For example, a prevalence of 25% implies that 48 laparoscopies need to be performed to obtain an extra pregnancy.

There are no RCTs that have assessed the value of surgery with advanced disease. Although advanced endometriosis is difficult to manage surgically, with a resulting low monthly fecundity rate (62, 63), removal of endometriomas can significantly improve pregnancy rates. Excision of the endometrioma is more effective than simple drainage and ablation of the cyst wall (64, 65). In a pooled analysis of data from two RCTs, the pregnancy rate was 60.9 % for excision versus 23.4% with the drainage and ablation technique (OR, 5.11; 95% CI, 2.03–12.85) (61). Because most endometriomas can be identified by ultrasonography, the number of laparoscopies needed to achieve results is the same. It is important in all surgery for removal of endometriomas that the patient be informed that the surgery may damage the ovary and reduce ovarian reserve (66, 67).

The value of excision of deeply infiltrating endometriosis solely to improve pregnancy is unclear and may adversely affect fertility (61). After initial unsuccessful surgery for endometriosis-associated infertility, in vitro fertilization is the best option rather than reoperation unless pain is still an important issue (68). Repetitive ovarian surgery has been shown to have a significant negative impact on in vitro fertilization outcomes (69).

▶ *In women with suspected endometriosis-related pain who desire future fertility, what is the initial treatment?*

Evidence suggests that pain associated with endometriosis can be reduced with the use of a variety of medications (progestins, danazol, combined OCs, nonsteroidal antiinflammatory drugs [NSAIDS], and GnRH agonists). Although there is no conclusive evidence that NSAIDS improve pain associated with endometriosis, these agents are reasonable options in appropriately selected patients (70).

A recent Cochrane review examined the use of combined OCs for endometriosis in 57 women allocated to either a combined OC or a GnRH analogue (71). No evidence of a significant difference in dysmenorrhea between the two groups was observed at 6 months after stopping treatment (OR, 0.48; 95% CI, 0.08–2.90).

Dysmenorrhea-associated withdrawal bleeding can be avoided with the use of extended-cycle pills. In a 2-year prospective study of women with endometriosis-associated dysmenorrhea that was not responsive to cyclic combined OCs, continuous combined OC administration was found to provide significant pain reduction from baseline ($P<.001$) (72). If the initial therapy fails in patients with suspected endometriosis, a diagnostic laparoscopy to confirm the presence of endometriosis may be offered. Alternatively, empiric treatment with another suppressive medication may be offered.

The need for laparoscopy in the diagnosis or treatment of pelvic pain secondary to suspected endometriosis has been the subject of debate (9). Arguments against the requirement to perform surgery to definitively diagnose endometriosis include the imprecision of surgical diagnosis as well as the inherent risks of surgery.

In a woman with pelvic pain, diagnostic evaluation should include a thorough history and physical examination to rule out other gynecologic causes of pain. Nongynecologic causes of pain, such as irritable bowel syndrome, interstitial cystitis, and urinary tract problems may be ruled out by appropriate testing and referrals. Consideration also should be given to pelvic ultrasonography, complete blood count, urinalysis, and endocervical testing for gonococcal and chlamydial infection if signs and symptoms warrant.

A randomized controlled, double-blind clinical trial has shown that after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with OCs and nonsteroidal antiinflammatory drugs, empiric therapy with a 3-month course of a GnRH agonist is appropriate (9). This approach is associated with clinically and statistically significant improvement in dysmenorrhea, pelvic pain, and pelvic tenderness. It is important to explain to the patient that response to empiric therapy does not confirm the diagnosis of endometriosis.

Comparing costs of empiric medical management versus definitive surgical diagnosis is more difficult to address. Although there is a lack of well-designed studies that compare the actual costs between the two approaches, it has been estimated that the cost of 3 months of empiric therapy is less than a laparoscopic procedure (73).

▶ *In women with pain, a known history of endometriosis, and desire for future fertility, what medical options are available?*

In these patients, NSAIDS or combined OCs can be offered as discussed previously. In patients with known endometriosis and dysmenorrhea, in addition to OCs, oral or depot medroxyprogesterone acetate (DMPA) are

effective compared with placebo and are equivalent to other more costly regimens. A large RCT showed combined OCs to be more effective than placebo (74). If they fail, there are three other forms of medical therapy that may be appropriate: progestins, GnRH agonists, and androgens. Oral norethindrone acetate and subcutaneous DMPA have been approved by the U.S. Food and Drug Administration (FDA) for treatment of endometriosis-associated pain. Two RCTs have shown that subcutaneous DMPA was equivalent to GnRH agonists in reducing pain with substantially less bone loss (75, 76). The bone loss that occurred with DMPA returned to pretreatment levels by 12 months. Patients interested in achieving pregnancy in the short term may not be candidates for depot formulations given the delay in resumption of ovulatory cycles.

Intrauterine progestin use with the levonorgestrel intrauterine system also has been shown to be effective in reducing endometriosis-associated pelvic pain. Three-year follow-up data showed a persistent benefit of the levonorgestrel intrauterine system (77), although approximately 40% of patients discontinued use because of unacceptable irregular bleeding, persistent pain, or weight gain. In an RCT comparing a GnRH agonist and the levonorgestrel intrauterine system, there was no significant difference between the two groups in control of pain (78). The levonorgestrel intrauterine system is not approved by the FDA for treatment of endometriosis-associated pain.

Danazol is an androgenic drug that has been used for the treatment of endometriosis-associated pain. Although highly effective, Danazol has a side effect profile, which includes acne, hirsutism, and myalgias, that is more severe than other drugs available.

Gonadotropin-releasing hormone agonists are highly effective in reducing the pain syndromes associated with endometriosis (79). However, they are not superior to other methods such as combined OCs as first-line therapy (71). Gonadotropin-releasing hormone agonists may have significant side effects, including hot flushes, vaginal dryness, and osteopenia. Osteopenia has been shown to be reversible with short-term use, but may not be with long-term use or use of multiple cycles (80). As with other suppressive therapy, recurrence of symptoms is common after the medication is discontinued. The recurrence rate at 5-year follow-up, after discontinuing GnRH agonist treatment, ranges from 53% to as high as 73% in women with advanced disease (81). There may be an option for prolonged use of the GnRH agonist for up to 1 year if add-back therapy is used.

▶ *What are the advantages and disadvantages of an "add-back" regimen with the use of a GnRH agonist?*

When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH agonist-induced bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief. Add-back regimens (using either sex-steroid hormones or other specific bone-sparing agents) have been advocated for use in women undergoing long-term therapy (more than 6 months) (82). Such treatment strategies have included progestins alone, progestins and bisphosphonates, low-dose progestins, and estrogens (58, 83, 86). The FDA has approved the daily use of norethindrone, 5 mg, as add-back therapy with a GnRH agonist. In a comparison of different add-back regimens, GnRH and norethindrone, with or without a low-dose estrogen (conjugated estrogens 0.625 mg daily), were found to decrease the side effect profile and maintain efficacy (87). If women do not tolerate the high-dose norethindrone, transdermal estradiol with medroxyprogesterone acetate can be used (transdermal estradiol, 25 micrograms per day plus medroxyprogesterone acetate 2.5 mg orally daily) (88). This regimen may not completely prevent bone loss and has not been approved by the FDA. It is recommended that daily calcium supplements (1,000 mg) be prescribed to patients using GnRH agonists with add-back therapy.

Add-back treatment does not diminish the efficacy of pain relief observed during 3 months or 6 months of GnRH agonist therapy (89). Therefore, the add-back regimen can be started immediately with the GnRH agonist. There appears to be no disadvantages to the use of an add-back regimen in combination with a GnRH agonist other than the incremental cost associated with the additional medication. However, a Cochrane review found little or no difference between GnRH agonist and other medical treatments for endometriosis, suggesting again that this regimen is not recommended as a primary treatment approach (90).

▶ *In women in whom conventional medical options for pain associated with endometriosis have failed, what other medical options are available?*

The FDA has only approved the use of a 12-month course of GnRH agonist therapy. In patients who have responded well to previous GnRH agonist therapy, long-term treatment with add-back therapy has been reported (91). Patients receiving this treatment should be monitored appropriately for physical findings, bone density, and serum lipid parameters.

The use of aromatase inhibitors such as anastrozole or letrozole have been evaluated in women with chronic pain resistant to other forms of medical management or

surgical management. Typically these drugs are used with a progestin or combined OC to dampen the follicle-stimulating hormone release, which may lead to chronic ovarian stimulation. These drugs have been reported to be efficacious in observational trials only with no controls (92, 93). Although promising, there are insufficient data to recommend their routine use (94, 95).

▶ *In women with endometriosis-related pain who desire future fertility, how effective is surgical therapy?*

In the first randomized, double-blind controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis, 63 patients were assessed 6 months after surgery, at which time the randomization code was broken and they were assessed again after another 6 months (96). At 6 months, 20 out of 32 patients (62.5%) reported symptom improvement or relief that was significantly different from 7 out of 31 patients (22.6%) in the expectant group. In this study, surgical therapy was least effective for stage 1 (minimal) endometriosis. In a similar double-blind RCT of patients with endometriosis of all stages, 80% of patients had symptomatic improvement 6 months after surgery versus 32% of patients in the expectant management group (97). The lower nonresponse rate in this study was attributed to the fewer number of patients with stage 1 disease.

In a follow-up of a large number of patients after surgical removal of endometriosis, the chance of requiring further surgery was 36% (98). In this study patients were monitored for an average of 3 years (range 2–5 years). At reoperation for recurrent chronic pain many patients had no visible endometriotic lesions. In a recent study, patients with all stages of endometriosis that had surgical removal of their lesions had a 21%, 47%, and 55% reoperation rate at 2, 5, and 7 years of follow-up, respectively (99). The only variable that predicted reoperation was the age of the patient at the time of the index surgery, with younger patients having a higher probability of reoperation. There is significant short-term improvement in pain after conservative surgical treatment; however, as with medical management, there is also significant recurrence rate of pain.

▶ *What is the role of neurectomies in the management of pain associated with endometriosis?*

Several randomized trials have demonstrated the lack of efficacy of uterosacral nerve ablation as an adjunct to surgical management of endometriosis (100, 101). Presacral neurectomy has benefit for midline pain only. This procedure is associated with potential postoperative side effects of constipation and urinary dysfunction (102).

▶ *How should endometriomas be managed in women who desire future fertility?*

Endometriomas are thought to be the result of progression of endometriotic lesions on the ovary that form cystic structures. They are invariably firmly attached to the ovary and the normal ovarian cortex where oocytes are embedded. Therefore, removal of the cyst always involves the risk that normal tissue also will be removed. These cysts may cause pain and infertility and they are associated with an increased risk of torsion and rupture. There is a small risk of malignancy associated with an endometrioma (103, 104). Levels of CA 125 may be increased in the presence of a benign endometrioma.

Although ultrasonography has a high diagnostic accuracy for endometriomas, it is recommended that endometriomas be removed in women without a previous diagnosis of endometriosis in order to obtain histologic confirmation that the cyst is benign. Some societies recommend removal if the cyst is more than 3 cm (105). Recurrent endometriomas are common. Further ovarian surgery needs to be considered on a case-by-case basis because reoperation may result in reduced or total loss of function of the ovary.

A prospective RCT has shown that laparoscopic excision of endometriosis has marked benefits over laparotomy with respect to analgesic requirement and recovery (106). Simple drainage of an endometrioma is associated with a high recurrence rate (61). Excision of the cyst compared with drainage and coagulation of the cyst wall is associated with lower recurrence of pain symptoms and cyst formation as well as a higher pregnancy rate (107).

▶ *What is the role of preoperative or postoperative medical suppressive therapy?*

There are no data that support the use of preoperative medical suppressive therapy (108). However, postoperative medical treatment could be useful when residual disease is expected, when pain is not relieved, or to extend the pain-free interval after surgery. Some studies support the use of postoperative GnRH agonists to extend the period of pain relief (109). In a randomized, controlled trial of an intranasal GnRH agonist, the median time to requirement of additional therapy after the GnRH agonist was discontinued was more than 24 months in the treated group versus 11.7 months in the nontreated group (110). The disadvantage of GnRH agonist therapy is the temporary nature of its benefit after discontinuation of the drug (111). In a 2004 Cochrane review, the use of perioperative medical therapy for women with endometriosis did

not demonstrate any long-term benefit (111). Long-term use of the agonist may be more beneficial but with associated long-term side effects and costs.

Combined OCs have been investigated as potential postoperative medical suppressive therapy, with the advantages of low cost, few side effects, and potential long-term use. A systematic review of combined OC use for postoperative prevention of symptom recurrence included six prospective studies, four of which were RCTs (112, 113). Results demonstrated the efficacy of long-term (at least 24 months) OC use on reducing endometrioma recurrence as well as a reduction in the frequency and severity of dysmenorrhea. The main conclusion is that while patients are taking combined OCs, symptoms are well controlled. Previous users do not seem to have a persistent effect. No difference in efficacy was reported between continuous and cyclic combined OCs.

The levonorgestrel intrauterine system has been used postoperatively for the treatment of endometriosis-associated pain. Both a small RCT and a Cochrane review concluded that the levonorgestrel intrauterine system reduces dysmenorrhea in women after endometriosis surgery (114, 115).

▶ *In asymptomatic women in whom endometriosis is discovered incidentally, what is the probability of regression or progression of disease?*

It is difficult to predict the long-term effect of endometriosis on an individual woman. There are no data to support use of medical treatment to prevent progression of the disease. Surgical treatment of incidentally found endometriosis at laparoscopy performed for other reasons needs to be decided on an individual basis.

There is little systematic research regarding either the progression of the disease or the prediction of clinical outcomes. The presence of endometriosis among asymptomatic patients being treated for infertility varies between 20% and 50% suggesting that it may not always be pathologic (116). In an RCT, a second-look laparoscopy was performed at 1 year after the diagnostic laparoscopy in all symptomatic control patients. These patients were those who were randomized to the nontreatment arm at the initial laparoscopy. This second laparoscopy revealed 7 patients (29%) showing disease progression, 7 patients (29%) showing disease regression, and 10 patients (42%) having static disease (96, 117). In another RCT, a second look at laparoscopy in the control untreated group, revealed that 8 out of 18 patients (45%) showed disease progression, 6 patients (33%) had disease that was unchanged, and 4 patients (22%) had disease that improved from their original surgery (97).

▶ *In patients with pain arising from known endometriosis affecting nonreproductive organs, what is the evidence for the efficacy of medical therapy for these symptoms?*

Extrapelvic endometriosis has been reported in a variety of sites, including the upper abdomen, the diaphragm, the abdominal wall (particularly the umbilicus), the perineum (episiotomy scar), and the thorax (118, 119). In addition, endometriosis may invade the full thickness of the rectum, large and small bowel, ureters, or bladder. The symptoms that are associated with endometriosis at these sites vary depending on location and depth of infiltration and include women with cyclic episodes of gross hematuria, hematochezia, and hemoptysis. Although a number of therapeutic approaches have been used for women with presumed extrapelvic endometriosis, the reported efficacy of ovarian suppression with a GnRH agonist appears to support it as the first line of therapy (120–122) except in cases of obstruction of the ureter or bowel, which are best treated surgically. Even in some cases of rectovaginal endometriosis, suppressive medical therapy may alleviate pain (61). Experience with managing these cases is limited to case series, often from a single center.

▶ *In women who do not desire future fertility and in whom conservative medical and surgical management have failed, how efficacious is definitive therapy for endometriosis?*

Hysterectomy, with bilateral salpingo-oophorectomy, often is regarded as definitive therapy for the treatment of endometriosis associated with intractable pelvic pain, adnexal masses, or multiple previous conservative surgical procedures. Based on the results of a retrospective analysis of women monitored for a mean duration of 58 months after hysterectomy, ovarian conservation was associated with a 62% likelihood of recurrent symptoms and a 31% chance of requiring additional surgical treatment (123). In the same study, women who underwent bilateral adnexectomy had a 10% chance of recurrence of symptoms and only a 4% likelihood of additional surgery. The authors also demonstrated that the relative risk for recurrence of pain after total abdominal hysterectomy was 6.1 (95% CI, 2.5–14.6) with ovarian preservation when compared with women who have their ovaries removed. The relative risk of additional surgery was 8.1 (95% CI, 2.1–31.3) with ovarian conservation. The limitation of this study is that it is unclear if the endometriosis was removed at the time of hysterectomy.

Similar results were seen in a more recent study of 120 patients who underwent excision of the endometriosis and hysterectomy with or without oophorectomy (99). These patients were monitored for a median duration of 7.6–11 years. Most patients did not require reoperation, even with conservation of the ovaries. Therefore, in patients with normal ovaries, a hysterectomy with ovarian conservation and removal of the endometriotic lesions should be considered.

▶ *Can patients have recurrent symptoms after hysterectomy and oophorectomy?*

Symptoms may recur in women even after hysterectomy and oophorectomy. Endometriosis may recur in up to 15% of women whether or not the patients are treated with estrogen therapy after bilateral oophorectomy (124). Consequently, hormone therapy with estrogen is not contraindicated after definitive surgery for endometriosis. Although the true rate of recurrence is unknown, in patients with recurrent symptoms undergoing a surgical procedure, endometriotic lesions may be demonstrated. The most common site of recurrent lesions is the large and small bowel (125). These lesions were likely present at the time of surgery and not excised. These lesions can be considered persistent disease rather than recurrent disease. Persistence of disease in hypoestrogenic states is most likely due to local expression of aromatase activity. Treatment is difficult and often requires surgery. The use of a GnRH agonist in this situation of hypoestrogenemia would not seem to be of benefit. Aromatase inhibitors may be considered but are not uniformly effective (126).

▶ *What is the role of hormone therapy after definitive surgery for endometriosis-associated pain?*

Currently, there are limited data on the timing of estrogen therapy after hysterectomy with bilateral salpingo-oophorectomy for endometriosis. It appears there is no advantage, in terms of recurrence rate, in delaying estrogen treatment after surgery (124, 127). There are limited data to indicate that hormone therapy may stimulate the growth of residual ovarian or endometrial tissue after total hysterectomy and bilateral salpingo-oophorectomy if all visible disease was removed (128). There is also a concern about the possibility of estrogen-induced malignant transformation in residual endometriosis implants (129). This has led some health care providers to recommend the routine addition of a progestin to the estrogen therapy. However, there is no outcomes-based evidence to support this recommendation.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Transvaginal ultrasonography is the imaging modality of choice when assessing the presence of endometriosis.
- Medical suppressive therapy improves pain symptoms; however, recurrence rates are high after the medication is discontinued.
- There is significant short-term improvement in pain after conservative surgical treatment; however, as with medical management, there is also a significant rate of pain recurrence.
- Medical suppressive therapies such as OCs or GnRH agonists for endometriosis-associated infertility are ineffective.
- Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude of improvement is unclear.
- Excision of an endometrioma is superior to simple drainage and ablation of the cyst wall.
- When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH agonist-induced bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- After an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with OCs and NSAIDS, empiric therapy with a 3-month course of a GnRH agonist is appropriate.
- In patients with known endometriosis and dysmenorrhea, OCs and oral norethindrone or DMPA are effective compared with placebo and are equivalent to other more costly regimens.
- Long-term (at least 24 months) OC use is effective in reducing endometrioma recurrence as well as a reduction in the frequency and severity of dysmenorrhea.

- Hormone therapy with estrogen is not contraindicated after hysterectomy and bilateral salpingo-oophorectomy for endometriosis.
- In patients with normal ovaries, a hysterectomy with ovarian conservation and removal of the endometriotic lesions should be considered.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- When medical management has failed, undergoing definitive surgical management is appropriate in those who do not desire future fertility.

Proposed Performance Measure

Percentage of patients with suspected endometriosis receiving OC therapy for pain management before more advanced therapies

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128. Matorras R, Elorriaga MA, Pijoan JI, Ramon O, Rodriguez-Escudero 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. (Level I)

129. Gucer F, Pieber D, Arikan MG. Malignancy arising in extraovarian endometriosis during estrogen stimulation. Eur J Gynaecol Oncol 1998;19:39–41. (Level III)

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985–January 2010. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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