Endometriosis Treatment & Management

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Approach Considerations

The dependence of endometriosis on the woman's cyclic production of menstrual cycle hormones provides the basis for medical therapy. Medications currently recommended include gonadotropin-releasing hormone (GnRH) agonists, progestins, oral contraceptive pills, and androgens. Each of these interrupts the normal cyclic production of reproductive hormones. There are some data supporting the use of aromatase inhibitors for refractory or recurrent endometriosis.

Medical vs surgical therapy

In women who wish to preserve their reproductive potential, the rates of recurrent pain symptoms are 44% with surgical management and 53% with medical management. [54, 55]

Endometriosis and subfertility

Peritubal and periovarian adhesions can interfere mechanically with ovum transport and contribute to subfertility. Peritoneal endometriosis has been postulated to contribute to subfertility by interfering with tubal motility, folliculogenesis, and corpus luteum function. Aromatase is believed to increase the prostaglandin E levels via increase in the cyclooxygenase-2 (COX-2) expression. Endometriosis may also cause subfertility by causing more sperm binding to the ampullary epithelium, thereby affecting sperm-endosalpingeal interactions. [56]

Medical treatment of minimal or mild endometriosis has not been shown to increase pregnancy rates. [57] Moderate to severe endometriosis should be treated surgically. [58]

Other options for achieving pregnancy include intrauterine insemination, superovulation, and in vitro fertilization. In a case-controlled study, pregnancy rates with intracytoplasmic sperm injection were not affected by the presence or extent of endometriosis. [59] Furthermore, other analyses have shown improvement with in vitro fertilization pregnancy rates with pretreatment of stage 3 and 4 endometriosis with gonadotropin-releasing hormone (GnRH) agonists.

Interval treatment

Some authorities believe that endometriosis should be suppressed prophylactically by continuous combined oral contraceptives, GnRH analogs, medroxyprogesterone, or danazol in order to cause regression of asymptomatic disease and enhance subsequent fertility. However, according to a Cochrane review, no benefit is derived from ovulation suppression in subfertile women with endometriosis who wish to conceive. [60]

A Cochrane review of interventions in women with endometriomata (cysts of endometriosis in the ovaries) before the use of assisted reproductive technology (ART) identified 4 trials with 312 participants could reach no conclusions regarding interventions for the management of endometriomata in women undergoing ART. [61]

In a 2015 systematic review and meta-analysis of the influence of endometriosis on ART outcomes from 36 studies (of 1346 articles), investigators found similar outcomes for live births between women with endometriosis who underwent in vitro fertilization and intracytoplasmic sperm injection and women without endometriosis. [62] However, women with severe endometriosis had lower live birth rates, clinical pregnancy rates, and mean number of retrieved oocyte relative to those without endometriosis. The investigators noted there remains not enough evidence to support recommending surgery routinely before women undergo ART. [62]

Surgical ablation of asymptomatic endometriosis has also been shown to improve fecundity rates on a 3-year follow-up. [58]

Recurrent pregnancy loss

Based on results from controlled prospective studies, no evidence indicates that endometriosis is associated with recurrent pregnancy loss, and no evidence indicates that medical or surgical treatment of endometriosis reduces the spontaneous abortion rate. [63]

Hormonal Therapy

The dependence of endometriosis on the woman's cyclic production of menstrual cycle hormones provides the basis for medical therapy. Thus, combination oral contraceptive pills (COCPs), danazol, progestational agents, and gonadotropin-releasing hormone (GnRH) analogues form the mainstay of medical therapy. All these treatments have similar clinical efficacy in terms of reduction in pain-related symptoms and duration of relief. See Medications.

Nonsteroidal anti-inflammatory agents (NSAIDS) have not been shown to have any benefit in placebo-controlled trials. [64] In a systematic review, aromatase inhibitors were shown to have promising results for pain relief when combined with either progestins, COCPs , or GnRH analogues. [65] However, the authors concluded that the strength of this inference was limited due to lack of sizeable trials. [65]

Combination oral contraceptive pills

COCPs act by ovarian suppression and continuous progestin administration. Initially, a trial of continuous or cyclic COCPs should be administered for 3 months. With pain relief, this treatment is continued for 6-12 months. Pregnancy rates following discontinuation of the pill

are 40-50%. This applies to a population unselected for stage and fertility status of the disease. Although few choices are available among individual formulations, note that the long-term efficacy of multiphasic preparations remains unproven.

Continuous noncyclical administration of COCPs, omitting the placebo menstrual tablets, for 3-4 months helps avoid any menstruation and associated pain. A study by Guzick et al examined a head-head-to-head comparison of Lupron and continuous oral contraceptives for the treatment of endometriotic pelvic pain; both were found to be equally effective. [66]

Women with endometriosis are at increased risk of epithelial ovarian cancer, and COCPs are believed to protect against this. [67]

Progestational agents

All progestational agents act by decidualization and atrophy of the endometrium.

Medroxyprogesterone acetate has proven efficacy in pain suppression in both the oral and injectable depot preparations. [68, 69] Oral doses of 10-20 mg/d can be administered continuously. The time to resumption of ovulation is longer and variable with depot preparations. Adverse effects include weight gain, fluid retention, depression, and breakthrough bleeding.

Megestrol acetate has been used in doses of 40 mg with similarly good results. [70]

The levonorgestrel intrauterine system (LNG-IUS) has been shown to reduce endometriosis-associated pain. [71] When inserted at the time of laparoscopic surgery, it has been found to reduce the recurrence of dysmenorrhea by 35%. [72]

Gonadotropin-releasing hormone analogues

GnRH analogues produce a hypogonadotrophic-hypogonadic state by downregulation of the pituitary gland. Goserelin and leuprolide acetate are the commonly used agonists. Efficacy is limited to pain suppression, and fertility rates may show no improvement. [73]

Winkel et al have claimed that GnRH therapy may lead to improvement in pain associated with endometriosis in 85-100% of women. [74] Furthermore, the pain relief is believed to persist for 6-12 months after cessation of treatment.

Treatment is usually restricted to monthly injections for 6 months. Loss of trabecular bone density caused by GnRH is restored by 2 years after cessation of therapy. [75] Other prominent adverse effects include hot flashes and vaginal dryness.

Add-back therapy and empiric therapy

Much interest has been shown in whether estrogen/progestin "add-back" therapy should be instituted to prevent osteoporosis and hypoestrogenic symptoms. Hormone replacement therapy preparations, progestins, tibolone maleate, and bisphosphonates have all been shown to be effective. [76, 77, 78, 79] Add-back therapy has been shown to prevent loss in bone density and to relieve vasomotor symptoms without reducing the efficacy of GnRH regimens. GnRH

agonists have been used for 12 months with norethindrone add-back therapy with good results. [80]

A clinical trial has shown that a 3-month empiric course of GnRH, based on a diagnostic algorithm without definitive laparoscopic diagnosis, is efficacious. [81] However, long-term effects of GnRH analogues on bone density in this population remain unproven. Therefore, add-back therapy remains the standard of care while the patient is on GnRH treatment. Also, empiric treatment without a firm diagnosis could result in unnecessary treatment in patients with chronic pelvic pain, whose condition could be due to other causes. In Ling's study, 13% of subjects were shown to not have endometriosis. [81]

GnRH therapy has also been proven to relieve the pain and bleeding associated with extrapelvic distant endometriosis. [82]

GnRH analogues vs danazol

A Cochrane review comparing GnRH analogues with danazol treatment showed no difference in improvement of dysmenorrhea, dyspareunia, pelvic pain, or pelvic tenderness. [83] Likewise, no difference in retrospective American Fertility Society (rRAFS) score was found at approximately 24 weeks' follow-up. In contrast, studies that evaluated total pain resolution showed greater benefit from GnRH analogues compared with danazol. Side-effect profiles differed, with greater frequency of hot flushes and vaginal dryness with GnRH analogues, whereas danazol treatment resulted in a greater frequency of weight gain, acne, and headaches.

Danazol

Danazol acts by inhibiting the midcycle follicle-stimulating hormone (FSH) and luteinizing hormone (LH) surges and preventing steroidogenesis in the corpus luteum. It is the most extensively studied agent for endometriosis.

Danazol has been shown to be as effective as any of the newer agents, but with a higher incidence of adverse effects. Its androgenic manifestations include oily skin, acne, weight gain, deepening of the voice, and facial hirsutism. Hypoestrogenic features due to danazol include emotional lability, hot flashes, vaginal dryness, and reversible breast atrophy.

The recommended dose is 600-800 mg/d. However, smaller doses have been used with success. [84, 85] In a small study of 21 patients, vaginal danazol (200 mg/d) was successful in relieving endometriosis-associated pain. [86]

Barrier contraception and ERT

Because of the possibility of virilizing changes in a female fetus, additional barrier contraception must be used while on danazol therapy.

The evidence for estrogen replacement therapy (ERT) in women with postsurgical menopause for treatment of endometriosis is unclear at the present time. [87]

Surgical Intervention

Surgical care can be broadly classified as conservative when reproductive potential is retained, semiconservative when reproductive ability is eliminated but ovarian function is retained, and radical when the uterus and ovaries are removed. Age, desire for future childbearing, and deterioration of quality of life are the main considerations when deciding on the extent of surgery.

Surgical efforts are aimed at removal of the endometrial implants and correction of anatomic distortions. Implants can be ablated using either laser energy or electrosurgical techniques.

Resection of the implants and adjacent peritoneum is considered the treatment of choice by some authors. A radical surgical approach involves total hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). This is generally reserved for women who have completed their family or for women with severely disabling pain that is unresponsive to more conservative approaches.

Conservative Surgery

With conservative surgery, the aim is to destroy visible endometriotic implants and lyse peritubal and periovarian adhesions that are a source of pain and may interfere with ovum transport. The laparoscopic approach is the method of choice for treating endometriosis conservatively. [88, 89]

Ablation can be performed with laser or electrodiathermy. Overall, the recurrence rate is 19% and is similar for all techniques. [90] Laparoscopic ablative surgery with bipolar diathermy or laser for endometriomas was shown to be effective for relieving pelvic pain in 87% of patients. [91]

Drainage vs laparoscopic cystectomy

Ovarian endometriomas can be treated by drainage or cystectomy. Laparoscopic cystectomy was found to yield better pain relief and pregnancy rates than drainage. [92, 93] Medical therapy with gonadotropin-releasing hormone (GnRH) agonists reduces the size of the cyst but does not influence pain relief. [94]

Ablation vs diagnostic laparoscopy

In the short term, the absolute benefit for women undergoing surgical ablation of endometriosis is 30-40% over women having only diagnostic laparoscopy. This benefit is reduced over time, and the reoperation rate is as high as 50%. [95] In cases of rectovaginal endometriosis, significant short-term pain relief was reported by up to 80%, but at 1-year follow-up, 50% required analgesics or hormones for pain relief. During postoperative treatment, GnRH analogues resulted in significantly reduced pain scores in women who received treatment for 6 months.

Tubal flushing with oil-soluble media has been shown to improve pregnancy rates in women with endometriosis-associated infertility. [96]

Presacral neurectomy and laparoscopic uterine nerve ablation

Presacral neurectomy is used to relieve severe dysmenorrhea. The nerve bundles are transected at the level of the third sacral vertebra, and the distal ends are ligated. Vascular injury to the middle sacral artery and vein is a potential complication, and some authors advocate prophylactic ligation. Also, constipation is a long-term adverse effect (94%) of this procedure and should be considered while deciding whether to perform this procedure.

Nodularity of the uterosacral ligaments may contribute to dyspareunia and low back pain. The transmission of neural pathways is via the Lee-Frankenhäuser plexus. Laparoscopic uterine nerve ablation (LUNA) is performed to interrupt the pain fibers. Potential complications of this procedure include uterine prolapse and pelvic denervation. A systematic review of trials of LUNA found no advantage in terms of pain relief when compared to placebo. [97] However, when combined with laparoscopic ablation, LUNA significantly reduced pain attributed to endometriosis. [54] In patients with subfertility, tissue ablation significantly increased the cumulative pregnancy rate. [58] A Cochrane review failed to show any benefit from either LUNA or presacral neurectomy. [98]

Postoperative adjunctive hormone therapy

For patients with mild disease, postoperative adjunctive hormonal treatment has been shown effective in reducing pain but has no impact on fertility. GnRH analogues, danazol, and medroxyprogesterone have all been found to be useful for this indication. [99, 100, 101, 102] However, for severe endometriosis, the efficacy of preoperative or postoperative hormonal treatment has not yet been established.

Semiconservative Surgery

The indication for this semiconservative surgery is mainly in women who have completed their childbearing, are too young to undergo surgical menopause, and are debilitated by the symptoms. Such surgery involves hysterectomy and cytoreduction of pelvic endometriosis.

Ovarian endometriosis can be removed surgically, because one tenth of functioning ovarian tissue is all that is needed for hormone production. Patients who undergo hysterectomy with ovarian conservation have a 6-fold higher rate of recurrence compared to women who undergo oophorectomy. [6]

Medical therapy in women who have completed childbearing is equally efficacious for symptom suppression. [55, 103, 104]

Radical Surgery

Radical surgery involves total hysterectomy with bilateral oophorectomy (TAH-BSO) and cytoreduction of visible endometriosis. Adhesiolysis is performed to restore mobility and normal intrapelvic organ relationships.

Ureteric obstruction may warrant surgical release or excision of a damaged segment. Bowel obstruction may require a resection anastomosis or a wedge resection if the obstruction is confined to the anterior rectosigmoid.

Endometriosis may recur in 15% of women after extirpative surgery, irrespective of whether estrogen-replacement therapy (ERT) is given postoperatively. [105] ERT can be instituted safely immediately after surgery, especially in younger women who face the prospect of accelerated bone loss and vasomotor symptoms. [105, 106] No trials have reported the use of estrogen plus progestin therapy with respect to estrogen therapy alone postoperatively. However, theoretically, the addition of a continuous progestin could decrease the regrowth of endometriosis.

Prevention

No current methods of prevention are known. Some evidence suggests that rapid and aggressive medical or surgical therapy can arrest progression, especially when the disease is caught in the early (minimal to mild) stages.

Early and prolonged use of oral contraceptive pills, pregnancy, and breast-feeding seem to afford some degree of protection against this disease.

Consultations

Treat patients with endometriosis in consultation with a physician experienced in the diagnosis and management of this condition and its complications, such as an obstetrician/gynecologist. If extensive disease is present, specialists in reproductive endocrinology, urology, colorectal surgery, and even gynecologic oncology may be required.

Any postpubertal patient going to the operating room for acute or chronic pelvic/abdominal pain could have endometriosis, therefore, consultation with a physician having the experience to recognize, diagnose, and treat this disease is prudent. Conservation of future fertility may be dependent on the conservative and meticulous surgical approach of an expert reproductive surgeon.

A study by Mu et al examined the prospective association between laparoscopically confirmed endometriosis and subsequent coronary heart disease among 116,430 women in the Nurses' Health Study II from 1989-2009. The study found that laparoscopically confirmed endometriosis was associated with increased risk of coronary heart disease. Women with endometriosis were 1.52 times more likely to have a myocardial infarction, 1.91 times more likely to develop angiographically confirmed angina, and 1.35 times more likely to need coronary artery bypass graft surgery, a coronary angioplasty procedure, or a stent. [107, 108]

Long-Term Monitoring

If the presumptive diagnosis is endometriosis and follow up is arranged, pain management can include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or narcotic analgesics. Start patients with classic symptoms of endometriosis and no reason to suspect another cause on medical therapy. Surgical diagnosis is not always required.

Lack of rapid response (within 1-2 cycles) to medical therapy should prompt a search for other causes of the patient's symptoms. Consider diagnostic laparoscopy if it has not been performed previously.

In patients who underwent surgery for endometriosis (or had endometriosis discovered during surgery for another indication), consider adjuvant medical treatment. At a minimum, place these patients on oral contraceptive pills until they are ready to conceive.

Endometriosis is progressive and can result in chronic pain and infertility. Gynecologic follow-up is advised.

Pediatric patients

Although most pediatric patients are not currently interested in becoming pregnant, subsequent fertility is likely a major concern. Evidence is mounting that early and aggressive therapy may alter the course of this disease. [109] Investigate moderate to severe dysmenorrhea that is unresponsive to NSAIDs and pelvic pain persisting longer than 3 months.