

Endometriosis

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I. INTRODUCTION

Endometriosis is the presence and growth of glands and stroma identical to the lining of the uterus in an aberrant location. Common symptoms of endometriosis are pelvic pain including dysmenorrhea, dyspareunia, and infertility. Endometriosis is most commonly found in the gravity-dependent areas of the pelvis, but can also involve the ovaries, bowel, bladder, or peritoneal surfaces. If the bladder or rectum is involved, symptoms referable to these structures may also be present. Distant sites of endometriosis have also been described.

II. ETIOLOGY

The exact pathogenesis of endometriosis remains unknown. Although there are several theories to explain the histogenesis of endometriosis, no single theory adequately explains the broad-ranged manifestations of this disease.

A. Retrograde Menstruation

The most popular theory described in 1927 by Sampson(1) is that endometriosis results from implantation of endometrial tissue fragments secondary to retrograde menstruation into the pelvic cavity. Indeed, endometriosis is most commonly found on structures near the tubal fimbria and gravity-dependent sites. Epidemiological studies, consistent with the theory that menstrual effluent in the peritoneal cavity is associated with endometriosis, have demonstrated that endometriosis is more common in women with cycle intervals less than 27 days in length, i.e., every 21 days vs. 28 days, and menses lasting longer than 7 days, as well as women with outflow obstruction of the genital tract. Clinical observations have been confirmed by experiments in monkeys that developed endometriosis when the cervix was transposed causing intraperitoneal menstruation with repetitive "seeding" of the peritoneal cavity, and the development of endometriosis(2). Dissemination of peritoneal endometrial fragments also occurs during surgical procedures, with endometriosis occurring in the subumbilical tissue and episiotomy sites.

B. Lymphatic and Vascular Dissemination

Endometriosis has been found in pelvic lymph nodes in women with this disease(3) . Pulmonary endometriosis and some other distant sites are best explained by hematogenous dissemination.

C. Coelomic Metaplasia

With the exception of coelomic metaplasia, the pathogenesis of endometriosis involves implantation of endometrial tissue in sites outside the uterine cavity whether by retrograde menstruation or by vascular, hematogenous, or operative dissemination. Although other forms of dissemination (hematogenous) are uncommon, retrograde menstruation occurs almost universally. Retrograde menstruation has been observed laparoscopically(5). Menstrual blood has been found in patients undergoing peritoneal dialysis(6).

D. Immune Defects

Endometriosis has been found in pelvic lymph nodes in women with this disease(3) . Pulmonary endometriosis and some other distant sites are best explained by hematogenous dissemination. The hypothesis that endometriosis is caused by an immunologic defect that allows implantation of endometrial fragments in the peritoneal cavity is attractive given the fact that most, if not all, women experience retrograde menstruation, yet only some women develop endometriosis. While retrograde menstruation may be considered to be a universal phenomenon among women, only those women a

theoretical defect(s) in their immune system develop endometriosis. Many studies have been conducted to explain the role of the immune system in the pathogenesis of endometriosis. Abnormalities of macrophages have been implicated in the development of endometriosis. One group of investigators(7) hypothesized that women with endometriosis have a greater proportion of larger, more aggressive macrophages that secrete prostaglandins, lysosomal enzymes, and growth factors that enhance the development of endometriosis.

E. Genetic

Women with a family history of endometriosis have a 7-fold increased risk of developing this disease than women with a negative family history(8). Furthermore, women with a positive family history of endometriosis in first degree relatives have a tendency to develop the disease earlier in life and have more advanced disease than women without a positive family history. The inheritance is likely transmitted by multiple factors, perhaps involving the immune system.

III. INCIDENCE

The true incidence of endometriosis is unknown. The incidence of endometriosis varies from 1 to 40% depending on the population studied and methods of diagnosis. Autopsy studies suggest an incidence of <1%, while 30% of asymptomatic patients undergoing laparoscopy for infertility are found to have the disease. In patients undergoing laparoscopy for pelvic pain, approximately 40% have endometriosis. Fertile, asymptomatic patients undergoing laparoscopy for elective tubal ligation have about a 2% incidence.

IV. MECHANISM OF DISEASE

A. Pain

Pelvic pain secondary to endometriosis is believed to be due to the inflammation and swelling of endometrial implants which is mediated by prostaglandins. Advanced disease with adhesions and large endometriomas may also induce pelvic pain. The poor correlation between the degree of pain reported by the patient and the degree of endometriosis found surgically has been well documented. One proposed explanation for this poor correlation involves the location of endometrial implants. It has been hypothesized that small implants located adjacent to nerve fibers or nondistensible (unlike the ovary) fibrous tissue may induce severe symptoms.

B. Infertility

Certainly advanced endometriosis with adhesions, which cause mechanical interference or tubal obstruction blocking ovum pickup, is a known cause of infertility. The role of minimal or mild endometriosis (revised AFS classification Stage I and Stage II disease) in infertility is less certain. Although the incidence of endometriosis diagnosed by laparoscopy is higher in women with infertility than fertile women and fecundity rates in women with endometriosis tend to be lower than fecundity rate in the general population, long-term cumulative pregnancy rates are similar in women with minimal and mild endometriosis treated with expected management (no treatment). There have been several mechanisms proposed by which endometriosis may cause infertility other than mechanical interference as noted above.

1. Prostaglandins. Prostaglandins secreted by endometrial implants have been found in increased concentrations in peritoneal fluid and have been implicated in affecting tubal motility, ovulation, and corpus luteum function. These findings have not been universally confirmed and, therefore, it is not established that women with endometriosis have higher level of prostaglandins in peritoneal fluid compared with other infertile women.

2. Peritoneal Macrophages. As noted previously, the increased activation of macrophages, possibly an immunological defect, has been associated in women with endometriosis. These activated macrophages may adversely affect sperm function or sperm-ovum interaction. Macrophages also secrete cytokines, such as interleukin-1, which may perpetuate the inflammatory process. Endometriosis has been postulated to induce ovulation defects and luteinized unruptured follicle (LUF) syndrome, but this has not been confirmed.

3. Autoimmune Antibodies. The prevalence of peripheral autoimmune antibodies, i.e., antiphospholipid antibodies, may be increased in patients with endometriosis which has been described as a mechanism for implantation failure and pregnancy loss(9).

4. Ovulatory Dysfunction. Approximately 15% of women with endometriosis will have a coincidental ovulatory defect with alterations in LH excretion and luteal phase defects. Unfortunately, none of these explanations for the role of endometriosis in infertility have been confirmed.

5. The Integrin Story. Integrins are a family of ubiquitously located cell adhesion molecules that enable some types of cells to adhere to each other. Variable patterns of integrin expression in human endometrium have been demonstrated during the menstrual cycle. Specifically one integrin, $\alpha\beta_3$ vitronectin receptor commonly referred to as Beta-3 (β_3), is expressed in endometrial epithelial cells only after day 19 of the normal menstrual cycle and corresponds to the beginning of the putative window of implantation. Lessey and colleagues(10) have suggested that women with luteal phase defects have reduced β_3 expression in the endometrium during this window of implantation (days 20 to 24) and, therefore, defective uterine receptivity. This same group studied integrin expression in 241 women with and without endometriosis, all of whom had in-phase mid-luteal histology, and found that the diagnosis of endometriosis correlated closely with a lack of β_3 expression. Furthermore, the "defect" in integrin expression was associated with nulliparity, was inversely related to the stage of disease, and occurred despite in-phase mid-luteal histology(11).

V. CLINICAL MANIFESTATIONS AND DIAGNOSIS

Endometriosis classically presents with symptoms of pelvic pain and/or infertility. The chronic pelvic pain usually presents as secondary dysmenorrhea and/or dyspareunia. However, approximately one-third of patients with endometriosis are asymptomatic, with the disease being discovered incidentally during an abdominal operation or visualized at laparoscopy for an unrelated problem.

Clinicians have appreciated the paradox that the extent of pelvic pain is often inversely related to the amount of endometriosis in the female pelvis. Women with large, fixed adnexal masses sometimes have minor symptoms, while other patients with only a few small foci of peritoneal implants may experience moderate to severe pain.

A. Symptoms

1. Pelvic Pain - related to the swelling and extravasation of blood in endometrial implants, believed to be mediated by prostaglandins.

2. Infertility

3. Abnormal bleeding - 15-20% of patients have premenstrual spotting or heavy menses. Tendency towards shorter cycle lengths and longer duration of menses.

D. Signs

1. Posterior cul-de-sac nodularity - palpable on rectovaginal examination, best performed on first day of menses.
2. Adnexal tenderness, ovarian enlargement.
3. Mulberry spot - vaginal or cervical bluish discoloration secondary to endometriosis.

D. Diagnostic tests

1. CA-125 - a cell surface antigen found on derivatives of the coelomic epithelium and a useful marker for epithelial ovarian CA, is elevated (>35 U/mL) in about one-third to one-half of women with AFS Stage III or IV endometriosis, but are frequently normal in Stage I or II disease. As a screening test, CA-125 lacks sensitivity and specificity, and therefore, is not useful in diagnosis. However, it may be helpful in certain cases to document recurrence.
2. Sonography - may be helpful for confirmation if pelvic examination is suspicious for the presence of an endometrioma. Sonography shows cystic structure with low-level homogenous internal echoes, but differentiation between endometriosis and corpus luteum cysts is not predictable.
3. CT/MRI - may be helpful if adnexal masses are present.

D. Laparoscopy

Endometriosis is classically a black-powder burn or brown color; however, the appearance is variable with lesions being red, black, blue, white, or clear. Endometriosis has been found in 6-13% of biopsies of normal appearing endometrium from infertile patients(12). Because other lesions can mimic endometriosis, a biopsy should be considered to establish the diagnosis of endometriosis.

VI. CLASSIFICATION SYSTEM

Throughout the years, there have been several attempts to classify endometriosis based upon operative findings. Currently, the most widely used classification scheme is the revised American Fertility Society (renamed American Society for Reproductive Medicine) classification of endometriosis published in 1985(13). There are weaknesses with all classification systems because the grading of endometriosis is subjective and often based upon the operator's experience. The current classification also fails to adequately differentiate between pelvic endometriosis with and without bowel involvement. In 1993, the American Fertility Society (ASRM) published a second form for classification of endometriosis in the presence of pelvic pain(14).

VII. NATURAL HISTORY

Endometriosis is a chronic and often times progressive disease, although the rate of progression varies widely among women. The recurrence rate of endometriosis is approximately 5-20% per year reaching a cumulative rate of approximately 40% after 5 years.

CONTINUE>>

Endometriosis/Adenomyosis (continued)

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VIII. MANAGEMENT

Management of endometriosis may be performed in the following ways: expectant management, medical treatment, surgical treatment, or any combination thereof. The type of treatment is dependent upon many factors including the severity of the symptoms, the type of symptoms (pain and/or infertility), the location of endometriosis, and the stage of the disease at the time of diagnosis.

A. Medical Treatment

In the medical management of pain (pelvic pain, dysmenorrhea, and dyspareunia) associated with endometriosis, prostaglandin inhibitors and hormonal therapy are commonly used. Endometriosis has been shown to have estrogen, progesterone, and androgen receptors and is noted to thrive in an estrogenic state. Barrier contraceptives are recommended during hormone therapy except for patients receiving OCPs. Medical treatment for pelvic pain, dysmenorrhea and dyspareunia associated with endometriosis has been successful, although symptomatic improvement may be short-term. Medical therapy for infertility is not of proven value. Specifically, fertility in patients with Stage I and II disease (revised AFS classification) does not differ whether expectant management, medical or surgical therapy is employed.

Medical management of endometriosis may be used for:

- * Primary therapy
- * Presurgical adjunctive therapy
- * Postsurgical therapy
- * Treatment of recurrent disease

1. Combined Estrogen-Progestin. Low-dose estrogen combination oral contraceptive pills suppress FSH and LH and endogenous estrogen production. Administered in a continuous or cyclic manner, they often relieve mild to moderate pelvic pain in patients with mild disease. The reduction of menstrual flow may also, theoretically, lessen the amount of reflux menstruation and thereby reduce the progression of the disease. The use of OCPs is also referred to as a "pseudopregnancy" regimen due to the high estrogen/progestin dosage. While OCPs are somewhat effective in relieving pain, post therapy pregnancy rates are only 40-50%.

2. Progestin Only. Progestational agents such as medroxyprogesterone acetate 10-30 mg/d orally or 150 mg/q 3 months intramuscularly in depot form inhibits FSH and LH, decreases estrogen production, and produces endometrial decidual change. Significant pain relief results; however, frequent breakthrough bleeding and occasional depression limit the usefulness of this drug. Progestin therapy is also not useful in patients attempting to conceive due to the induced amenorrhea and anovulation.

3. Danazol. Danazol, a derivative of 17 α -ethinyl testosterone produces an androgenic/low-estrogen environment that results in atrophy of endometriotic implants. It suppresses the midcycle LH and FSH surge, decreases ovarian steroidogenesis, and reduces endometrial aggression by a direct effect on the cells. Pain relief is frequently achieved with 200-400 mg/b.i.d. for 3-6 months. Common side effects include weight gain, fluid excess, decreased breast size, oily skin, facial hair, deepening of the voice, atrophic vaginitis, hot flashes, fatigue, muscle cramps, emotional lability, and headaches. There is also an elevation in cholesterol and LDL cholesterol and a reduction in HDL levels. Mild elevations of liver function tests have also been reported. Most changes are reversible and regress when medication is discontinued.

4. Gonadotropin Releasing Hormone Agonists. GnRHa are a synthetic derivative of the native decapeptide GnRH. Substitutions at the 6 and 10 positions create an agonist with greater potency than the naturally occurring hormone. Agonist may be delivered as a daily subcutaneous injection, monthly depot form as an injection or implant, or as a nasal spray. After a transient (2 weeks) stimulation, there is significant and sustained decrease in LH and FSH production with resultant hypoestrogenism. Intramuscular preparations (leuprolide acetate 3.75 mg or subcutaneous goserelin, 3.75 mg)

administered once monthly or nasal spray (Nafarelin, 200 mg) administered twice daily for 3-6 months provides both subjective and objective improvement of symptoms.

Most adverse events reported with GnRH agonists are similar to the symptoms that occur commonly during natural menopause and are related to hypoestrogenism. The most common side effect is hot flashes, vaginal dryness, and some sleep disturbance. Recently, the use of GnRH-agonists with ·add-back· therapy has been advocated for endometriosis-related pelvic pain. Friedman and Hornstein(16) studied 8 patients with moderate to severe pelvic pain who received leuprolide acetate depot, 3.75 mg IM every 4 weeks for 2 years, and ·add-back· therapy consisting of conjugated estrogens, 0.625 mg/d orally and medroxyprogesterone acetate 2.5 mg/d orally starting at month 3. They reported a significant improvement in pelvic pain during the study period without significant bone loss and a reduction in hot flashes in the study subjects. The basis for this therapy is the ·estrogen threshold hypothesis· described by Barbieri(17), that is, a concentration of estradiol exists which inhibits growth of endometriosis, yet partially prevents bone loss.

B. Surgical Treatment

Surgical therapy is generally employed for treatment of infertility, even though it is unproven at this time for Stage I and II disease. Since the diagnosis must be made laparoscopically and endometriosis is a progressive disease, however, it stands to reason that surgical treatment at the time of diagnosis is appropriate and cost effective unless there is a risk of injury to a pelvic structure, proper equipment is not available, or the surgeon is not trained in the surgical procedure.

Currently, there are four main treatment modalities used in the surgical management of endometriosis. While these methods are frequently used in combination with other modalities, they will be individually described. These methods are (1) mechanical, (2) electrosurgery, (3) endocoagulation, and (4) laser. Each method offers different advantages and disadvantages. Surgical therapy may consist of laparoscopy or laparotomy and may be considered to be conservative or definitive (TAH/BSO).

1. Mechanical. Mechanical surgical methods refer to the use of laparoscopic scissors and other traditional surgical instruments (graspers, forceps, clamps, etc.) through the endoscope. Because hemostasis must be maintained, the other methods described here must also be used.

2. Electrosurgery. Electrosurgery for endometriosis involves the use of electrical energy to fulgurate or excise endometriosis. Besides mechanical dissection, electrosurgery is the oldest surgical method for laparoscopic treatment of endometriosis. While endometriosis on the uterosacral ligaments and ovaries can be treated easily via both unipolar and bipolar cautery, the use of electrosurgery for even superficial lesions on bladder, bowel, and other vital structures, such as the ureter, is potentially dangerous. The experienced physician who understands the limits of the instrumentation must work quickly and safely, but the inexperienced surgeon who attempts the treatment of endometriosis on bowel, bladder, or over the ureter and who operates at a much slower rate over these vital structures must be exceedingly cautious in the use of electrocautery.

3. Endocoagulation. Endocoagulation is the surgical technique that was devised by Semm in Germany. Semm believes that the lower heat involved with endocoagulation compared with cautery reduces scar tissue formation. While depth of penetration with the endocoagulator is not as great as with electrosurgery, it is not a precise system. Moreover, caution must still be exercised when the endocoagulator is used on the bowel or bladder, or over the ureters. Also important, the depth of penetration with endocoagulation may not be great enough to permit coagulation of deep implants of endometriosis.

4. Laser Laparoscopy. Lasers are advantageous in their ability to cut, coagulate, and vaporize tissue. In comparison with other various energy systems, the laser is more precise. Endometriosis can be vaporized and excised with the laser, and thus includes lesions over the bowel, bladder, ureters, and vessels. The most widely used laser for the treatment of endometriosis is the carbon dioxide laser, which is excellent for both cutting and vaporizing lesions. However, because of its low tissue penetration, the CO₂ laser is a poor instrument for coagulation. Its depth of penetration can be as little as 0.12-0.2 mm. Lateral distribution of energy is the least with this laser compared to other laser wavelengths.

The CO₂ laser has other limitations. The beam is transmitted through a bulky, heavy articulating arm. If any of the mirrors and lenses within the arm are out of alignment, the laser is rendered useless. As the laser cuts and vaporizes, smoke is generated that can obscure vision. Finally, the CO₂ laser is absorbed in fluid, thus losing its power when irrigating fluid is used or when the field is somewhat bloody.

Fiber Laser. To overcome some of the shortcomings of the CO₂ laser, other wavelengths have been used in the laparoscopic treatment of endometriosis. The three most common alternate lasers currently in use are the argon, potassium titanyl phosphate (KTP), and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers. These lasers can be passed through optical fibers, hence the name 'fiber lasers' (Table I). Data regarding pregnancy and pain relief after different laparoscopic surgical methods are variable. Of 50 patients treated with the argon laser in 1987, 92% of patients reported pain reduction. Of 270 patients with pelvic pain, 77% were still pain free after 1 year.

The reported results of pre-operative or postoperative hormonal therapy is conflicting. Nevertheless, clinical judgement supports combined therapy in certain circumstances.

Patients with severe or extensive endometriosis may benefit from a 4-6 week pre-operative course of GnRH agonists or Danazol to suppress inflammatory response and reduce vascularity, or a 12-week postoperative course to suppress microscopic disease. Patients with severe pain but no symptoms of infertility may benefit from postoperative oral contraceptives, GnRH agonists or Danazol in addition to surgical ablation of disease. This is particularly applicable in young women in whom preservation of childbearing potential is important.

Summary

In conclusion, medical and surgical options for management of women with endometriosis allow a variety of approaches that may be tailored individually to the patient, her desires for fertility, and the physician's experience. There is no one therapy or combination of therapies that is right for all women. Nonetheless, the clinician should have a thorough knowledge of the potentials and limitations for each therapeutic modality.

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