Pathophysiology and Management of Endometriosis

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Endometriosis is a common disease that affects up to 5 million women in the United States. Specifically the prevalence of endometriosis is 1 in 15 (7%) women of reproductive age, and there is an associated incidence of infertility in as many as 30% to 40% of cases. The precise physiologic mechanism for the development of endometriosis lesions in the pelvis and abdominal cavity has not been elucidated. Substantial evidence exists, however, that endometriosis is dependent on estrogen for continued growth and proliferation. Therefore, suppression of the hypothalamic-pituitary-ovarian axis with analogues of a gonadotropin-releasing hormone is being increasingly undertaken. Since the most effective resolution of endometriosis occurs after oophorectomy or onset of menopause, the hypoestrogenic state induced by GnRH analogues is of major significance for patients with active disease. Medical therapy for endometriosis is often used as primary therapy for symptomatic disease or as an adjunct to surgical management of pelvic pain or infertility.

Key words. Endometriosis; dysmenorrhea; menstruation; pain. (*J Fam Pract 1993; 37:68-75*)

Endometriosis is a disorder that affects as many as 5 million women in the United States. The pain and other symptoms can be severe and even incapacitating. The fact that the most severe disease sometimes occurs in women with the least extensive lesions underscores the perplexing nature of this disorder.[1–3] It is important for primary care physicians to understand the nature of endometriosis and the variability of its signs and symptoms, as the disorder may be the source of complaints that seem unrelated to the female reproductive system. Fortunately, during the past few years, pharmacologic and surgical therapies have been developed and refined, offering significant relief to the majority of women who suffer from this disorder, with substantial reductions in risk, inconvenience, morbidity, and overall cost. Primary care physicians can contribute to the care of these women by considering the diagnosis of endometriosis, reassuring the patient that effective therapies are available, seeking a definitive diagnosis, administering therapy when appropriate, and following the patient during the prescribed course of therapy.

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Epidemiology

Many physicians believe that the incidence of endometriosis has been increasing for the past 25 years.[1] The increase in the number of identified cases may be attributable, to some extent, to a heightened awareness of mild to moderate endometriosis, diagnosed by laparoscopy in the course of evaluations of infertility. Another possibility is that the increasing tendency of women to delay childbearing until their 30s and even 40s is associated with an increased incidence of endometriosis.[1] It is difficult to arrive at definitive conclusions, since there is no way to evaluate retrospectively the incidence of this disease at a time when advanced diagnostic techniques were not yet available.

Estimates of the percentage of cases of endometriosis found by laparoscopy or laparotomy in reproductive-aged women range from 5% to 15%[4]; many cases are diagnosed incidentally during procedures performed for other purposes. The incidence of endometriosis among infertile women is between 30% and 45%,[4] and has been as high as 68% in centers with laparoscopists who are

proficient at finding subtle endometriosis.[5] In one group of 1542 premenopausal white women, endometriosis was found in 25% of women with dysfunctional uterine bleeding, in 21% of women being investigated for infertility, in 15% of those being investigated for chronic abdominal pain, and in 6% of women undergoing laparoscopic sterilization.[3]

As there is a higher incidence of endometriosis in infertile women, questions of cause and effect inevitably arise. For example, does mild endometriosis cause infertility? Does treatment of asymptomatic endometriosis improve fertility? At present, these questions have engendered controversy,[6,7] although a reduction of active disease appears to enhance fertility, even in women with mild to moderate disease.[8]

Surgical therapy, specifically laparoscopic ablation, has been shown to improve fertility rates in patients with mild, moderate, and severe endometriosis.[8] Treatment of endometriosis includes laparoscopic ablation of endometrial implants, both deep and superficial, in stage I (minimal) and stage II (mild) disease. Stage III to IV disease may require more involved surgery, such as laparotomy. These surgical procedures may result in an improved environment for fertilization and establishment of pregnancy.[8] In patients with minimal disease, no therapy, or "observational management," has been shown to result in pregnancy rates comparable to those obtained with medical or surgery therapy.[9] Medical therapy has also led to improvement in fertility rates. Patients who receive medical therapy (hormonal GnRH therapy) must continue to use nonhormonal methods of contraception because GnRH agonists do not ensure against pregnancy.

Pathogenesis

Endometriosis is the presence and growth of the glands and stroma of the lining of the uterus, or endometrium, at an aberrant (heterotopic) location (Figure 1). Many questions remain regarding the cause of this poorly understood disorder. Although the exact cause of endometriosis remains elusive, each of the following hypotheses may represent a part of the total picture.

Retrograde Menstruation

The most widely held view of the cause of endometriosis involves seeding and implantation of endometrial cells at ectopic locations as a result of retrograde menstruation, or the flow of menstrual fluid backward through the fallopian tubes rather than forward through the cervix and outward through the vagina. Retrograde flow occurs in virtually all women to some degree. It is consistent with these observations that women in whom normal flow is obstructed have a higher incidence of endometriosis, as do women with histories of menstrual flow lasting longer than 7 days.

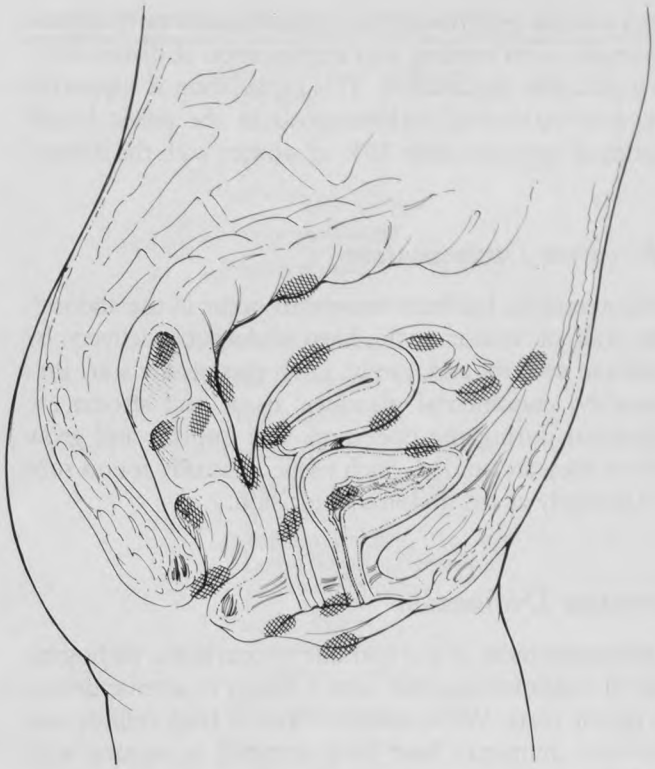

Figure 1. Common sites of endometriosis in the pelvis. Adapted from Droegmueller,[4] with permission of Mosby–Year Book.

Coelomic Metaplasia

Another way to account for the ectopic presence of endometrial tissue is the transformation of tissue at extrauterine locations. Rather than seeding the peritoneum with viable endometrial cells from within the uterus, the coelomic metaplasia hypothesis holds that epithelial cells in the abdomen and pelvis, which have a common embryologic origin with cells of the female reproductive system, retain the ability for multipotential development, and are induced to differentiate into endometrial cells.[10] Metaplasia is thought to occur as a result of induction by a stimulus such as exposure to menstrual debris or estrogen and progesterone.

Lymphatic and Vascular Metastasis

Endometriosis has been documented at locations as diverse as the spinal column, nose, forearm, thigh, and lung.[4] In these cases, hematogenous spread of viable

endometrial cells through the bloodstream or lymphatic channels, with seeding and implantation at distant sites, is a plausible explanation. This explanation is supported by observations of endometriosis in the pelvic lymph nodes of approximately 30% of women with the disease.

Iatrogenic Dissemination

Endometriosis has been known to occur in the abdominal wall of women who have undergone delivery by cesarean section, and, rarely, in an episiotomy scar. Presumably, endometrial glandular tissue and stroma are displaced during the operation, and implant and grow where they are seeded. Such tissue is usually found subcutaneously at the abdominal incision.

Immune Dysfunction

The involvement of the immune system in the pathogenesis of endometriosis has been a matter of intense debate in recent years. While abnormalities of both cellular and humoral immunity have been detected in women with endometriosis,[4] the results of such studies have been inconsistent. Anti-endometrial antibodies have been detected in the peripheral blood and peritoneal fluid of women with endometriosis, as have defects in local cell-mediated immunity.[4] The primary immune system defect appears to involve the population of monocyte–macrophages in the peritoneum. According to one hypothesis, women who do not develop endometriosis have early-stage monocytic macrophages in their peritoneal fluid. Women who develop endometriosis have more mature peritoneal macrophages that are larger and more aggressive, and which secrete substances such as prostaglandins, cytokines, and growth factors.[4] These compounds, typically secreted by activated macrophages, can cause the irritation and stimulation of growth associated with the other hypotheses described above.

Genetic Predisposition

A familial predisposition to endometriosis has been identified. In one study,[11] the prevalence of documented endometriosis in female siblings of 123 women with endometriosis was 5.8%, and the prevalence in the mothers was 8.1%. In contrast, the prevalence in the female siblings and mothers of the husbands of the 123 women with endometriosis was 1.0% and 0.9%, respectively.

In summary, while the specific cause of endometriosis is not known, several hypotheses have been developed that help explain many aspects of the disease. As with many other diseases, several factors may contribute to the clinical expression.

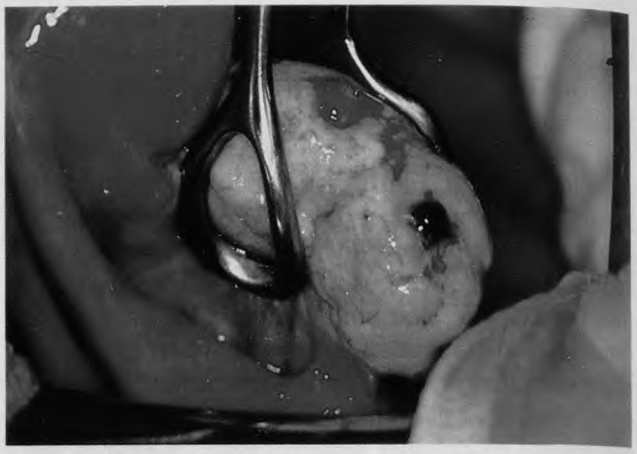

Figure 2. Implants of endometriosis may be seen as brown or blue-black nodules or as tiny, puckered hemorrhagic foci, referred to as "powder-burn" spots. Ovarian cysts that result from endometriosis are frequently filled with old blood and are often called "chocolate cysts" because of the color of the cyst components. These are termed endometriomas.

Pathology

Most endometrial growths are located in dependent portions of the female pelvis (Figure 1). In 2 out of 3 patients, the ovaries are involved; usually, the involvement is bilateral. Other common sites of involvement include the pelvic peritoneum over the uterus, the anterior and posterior cul-de-sacs, and the uterosacral, round, and broad ligaments. Other possible locations in the pelvis include the cervix, vagina, and vulva. Approximately 10% to 15% of cases involve the serosal surface of the rectosigmoid colon. If there is extensive scarring, endometriosis of the bowel may be difficult to differentiate grossly from a primary neoplasm of the large intestine.[4]

Appearance

The most common misconception among physicians regarding endometriosis is that the disease is identified by the presence of small, dark, blue-black berry-shaped lesions. In recent years, however, based on findings from laparoscopic examination of more subtle lesions, it has become clear that endometriosis may appear in a wide variety of forms (Figure 2). The color may vary from red to brown, black, white, or yellow, or the lesion may appear as a clear, pink, or red vesicle. The appearance

depends on the blood supply and the amount of hemorrhage and fibrosis in the lesions.

New lesions are sometimes blood-filled cysts that are less than 1 cm in diameter. The lesions may grow with time, and assume a brown color that accounts for the term "chocolate cyst" (Figure 2). Endometriotic lesions in a teenager may not have the typical darkened appearance because there has been less time for repeated episodes of hemorrhage and fibrosis.

Clinical Course

The classic patient with endometriosis is in her mid-30s, nulliparous and infertile, and has symptoms of secondary dysmenorrhea and pelvic pain. However, because the expression of the disease is so variable, the majority of women do not present with the classic clinical picture.[12] The clinical expression of endometriosis may be confusing and is often paradoxical. For example, even though the growth of ectopic endometrium is stimulated by physiologic levels of estrogen and progesterone, which accounts for the disease commonly occurring during the reproductive years, both low and high levels of these hormones may actually be therapeutic.[13] In addition, the severity of symptoms does not always correlate with the extent of disease.[1,3]

Koninckx et al[5] recently reported a 3-year prospective study of 643 women undergoing laparoscopies for infertility, pelvic pain, or both. The incidence of endometriosis was 68%, 71%, and 84%, respectively, in these patients. Although there was no correlation between the degree of pelvic pain and the total area of endometriosis, these investigators reported that women with pelvic pain had larger, more infiltrating lesions, that the depth of infiltration was the most important discriminator of pain, and that both the incidence of endometriomas (nonneoplastic masses containing endometrial tissue) and the depth of infiltration increased with the age of the patient.[5]

Symptoms

The primary symptom of endometriosis is pelvic pain; however, the differential diagnosis for this symptom is extensive (Table 1). The classic group of symptoms of endometriosis are cyclic pelvic pain, dysmenorrhea, dyspareunia, and infertility[14] (Table 2). In many cases, the disease is asymptomatic and is identified during an invasive procedure performed for an unrelated reason. Pelvic pain, when present, is cyclic in nature, correlating with the fluctuation of cyclic hormones.[13] The dysmenorrhea generally begins shortly before menstruation. The dyspareunia associated with endometriosis is described as a deep pain in the pelvis; it may be related to the immobility of the pelvic organs during intercourse or direct pressure on endometriotic lesions. The pain may continue for several hours after intercourse.

Other symptoms include abnormal bleeding, usually premenstrual spotting.[15] Ovulatory dysfunction may also occur: between 11% and 27% of women with endometriosis also have anovulation.[15] Other complaints, which are less common but may be quite troubling to the patient, are related to endometriotic involvement of the gastrointestinal or urinary tracts. Symptoms may include abdominal pain, constipation, diarrhea, urinary frequency, pain on defecation or urination, or hematuria.[12,15]

Table 1. Differential Diagnosis of Pelvic Pain

Complications of pregnancy
Abortion
Tubal pregnancy
Leiomyomas
Adenomyosis
Uterine perforation
Endometriosis
Pelvic inflammatory disease
Pelvic congestion syndrome
Ovarian sources
Tubal sources
Urinary tract origin of pain
Intestinal sources of pain
Appendicitis
Regional enteritis
Lower bowel malignancy
Intestinal obstruction
Vascular sources
Thrombophlebitis
Mesenteric occlusion
Orthopedic causes
Psychogenic causes

Based on data from Weingold.[12]

Table 2. Symptoms of Endometriosis

Common	Less Common
Cyclic pelvic pain	Abdominal pain
Secondary dysmenorrhea	Constipation
Dyspareunia	Diarrhea
Infertility	Urinary frequency
Abnormal bleeding	Pain on defecation
	Pain on urination
	Hematuria
	Bowel obstruction
	Hydronephrosis

Clinical Signs

The most common finding on physical examination of patients with endometriosis is a fixed, retroverted uterus with scarring, and tenderness posterior to the uterus.[12,15] Nodularity of the uterosacral ligaments and the cul-de-sac of Douglas may be palpated on rectovaginal examination.[2,12] In advanced cases, extensive scarring and narrowing of the posterior vaginal fornix may be found.[7,12] The speculum examination may reveal a small area of endometriosis on the cervix or upper vagina.[12] A pelvic examination performed during the immediate premenstrual period or on the first day of menstrual flow is most likely to identify the signs of endometriosis, since the cyclic changes are most pronounced at that time.[7,12]

Diagnosis

Noninvasive methods of diagnostic visualization, such as ultrasonography and magnetic resonance imaging, are not very useful for diagnosing endometriosis, especially in its limited stages, because of their lack of sensitivity.[7] Recently, interest has focused on measurement of serum levels of a cancer antigen (CA-125), which are elevated in most patients with endometriosis and which rise incrementally in advanced stages of the disease. CA-125 is present on the cell surface of epithelia of coelomic and müllerian origin, including endometrial tissue.[7] However, the CA-125 test has very poor specificity, as levels also rise with other diseases, including epithelial carcinoma of the ovaries. The test also lacks sensitivity, as levels are not elevated in patients with less advanced disease. Despite widespread interest, at present the test appears to have little clinical value for diagnosis of or screening for endometriosis.

The diagnosis of endometriosis is in most cases confirmed by direct laparoscopic visualization of the lesion(s) and the associated scarring and adhesions. It should be noted, however, that even laparoscopic visualization is dependent on several variables. For example, minimal lesions may not be immediately visualized; a double-puncture technique is preferable to the single-puncture technique; characteristics of the laparoscope as well as experience of the laparoscopist are also important variables.[7] Biopsy specimens retrieved through the laparoscope help to confirm the diagnosis. Criteria for classification of endometriosis as mild, moderate, or severe are shown in Table 3. The classification system of the American Fertility Society is based on a 20-point scale and includes four stages: minimal disease (stage I), mild disease (stage II), moderate disease (stage III), and severe disease (stage IV).

Table 3. Classification of Endometriosis

Clinical Findings
Mild Disease
•Scattered, superficial implants on structures other than uterus, tubes, or ovaries; no scarring
•Rare, superficial implants on ovaries
•No significant adhesions
Moderate Disease
•Involvement of one or both ovaries with multiple implants or small endometriomas (≤2 cm)
•Minimal peritubular or periovarian adhesions
•Scattered, scarred implants on other structures
Severe Disease
•Large ovarian endometriomas (>2 cm)
•Significant tubal or ovarian adhesions
•Tubal obstruction
•Obliteration of cul-de-sac, major uterosacral involvement
•Significant bowel or urinary tract disease

From Puleo JG, Hammond CB. Conservative treatment of endometriosis externa: the effects of danazol therapy. Fertil Steril 1983; 40:164–9. Reproduced with permission of the publisher, The American Fertility Society.

Management

Since the patient population, pathology, and clinical manifestations of endometriosis are highly variable, no single therapeutic approach is appropriate for all patients. Direct visualization is the only way to diagnose endometriosis and to determine the physical extent of the disease. This information is then integrated with the medical history and the patient's particular circumstances to arrive at an appropriate therapeutic approach.

Circumstances that need to be considered include the patient's desire to maintain fertility; a surgical option that may be appropriate for a 38-year-old woman with three children who does not wish to become pregnant may not be suitable for a 30-year-old woman who wants to begin a family. In general, therapy may be medical (ie, pharmacologic), surgical, or a combination of both.

Medical Therapy

The goal of hormonal treatment of endometriosis is to induce amenorrhea, resulting in an endocrine environment that does not stimulate growth of endometriotic lesions and may promote their regression. In a sense, hormonal therapy is titrated to amenorrhea. Medical therapy is usually administered as a 6- to 9-month course. Failure rates, usually defined as moderate to severe dysmenorrhea 6 months after the completion of therapy, have been as low as 7% to 27%.[16,17] Thus, many patients who remain asymptomatic several months after a course of therapy will not require follow-up laparoscopy. Those with recurrent disease, however, may require second courses or alternative therapy.

Danazol

Danazol has been available since the mid-1970s for the treatment of endometriosis. It is an anabolic steroid with mild androgenic effects; many of its side effects are related to these two properties. Danazol binds to androgen and progesterone receptors and to sex hormone-binding globulin; this latter effect causes a threefold increase in free testosterone levels. Doses of 800 mg/d produce amenorrhea and inhibition of ovulation within 4 to 6 weeks after the onset of therapy; the atrophic changes in the endometrium of a young woman taking danazol have the same appearance on biopsy as tissue taken from a postmenopausal woman.

Side effects of the hormone-induced "pseudomenopause" are seen in 80% of patients who take danazol; approximately 10% to 20% of women discontinue the drug because of side effects (usually the androgenic ones), which usually disappear on cessation of therapy.[16,18,19] Adverse symptoms include menopausal hot flushes, atrophic vaginitis, emotional lability, weight gain averaging 8 to 10 pounds, fluid retention, migraine headaches, dizziness, fatigue, depression, oily skin, facial hair, and deepening of the voice. In addition, danazol appears to lower levels of high-density lipoprotein (HDL) and raise levels of low-density lipoprotein (LDL).[20] These effects are important risk factors for atherogenesis, although their relevance, given the relatively short time frame of therapy for endometriosis (approximately 6 to 9 months), is not clear.

Gonadotropin-Releasing Hormone (GnRH) Agonists

Synthetic analogues of naturally occurring gonadotropin-releasing hormone (GnRH) are 60 to 150 times more potent than the naturally occurring substance and have longer half-lives.[20,21] After an initial increase in the release of luteinizing hormone and follicle-stimulating hormone, chronic administration of these agents results in specific suppression of gonadotropin secretion, with a secondary decrease in ovarian production of steroid hormones. The mechanism of action of GnRH agonists appears to be downregulation of target receptors.[20]

The two GnRH agonists approved for endometriosis are leuprolide acetate and nafarelin acetate. Because they are peptides, they cannot be given orally. Leuprolide is given as a monthly intramuscular injection; nafarelin is delivered by topical absorption through the nasal mucosa, with one spray in one nostril in the morning and another dose in the other nostril in the evening. The depot formulation of leuprolide acetate, allowing monthly intramuscular administration, has greatly simplified GnRH agonist therapy and facilitated compliance.[17]

Chronic use of a GnRH agonist produces dramatic reductions in serum estrone, estradiol, testosterone, and androstenedione similar to those seen in surgically castrated women.[22] The total serum estradiol levels and the free serum estradiol concentrations are 31% to 56% of those found in women taking danazol.[23,24] In addition to this more potent effect on suppression of steroid hormone levels, the GnRH agonists do not raise testosterone levels, as they have no effect on sex hormone–binding globulin. Thus, the androgenic side effects caused by danazol are not generally seen with GnRH agonists. Similarly, the GnRH agonists cause no significant changes in total serum cholesterol, HDL, or LDL levels.[20] For several reasons, then, GnRH agonists appear likely to replace danazol as the medical treatment of choice for women with endometriosis; in terms of convenience and patient compliance, the intramuscular depot form of leuprolide offers a clear advantage.[1]

The side effects associated with GnRH agonist therapy are those related to estrogen deprivation, as occurs in menopause: the most common are hot flushes, vaginal dryness, and insomnia. There is some indication that trabecular bone density in the spine may decrease during GnRH agonist therapy.[25] Such changes are thought to be partially or completely reversible with cessation of treatment.[26]

Therapy with a GnRH agonist results in improvement of symptoms of endometriosis in 75% to 92% of patients. Depending on the extent of disease, growth of endometriosis is arrested, diminished, or eliminated.[16,17,27–29] The rates of improvement are comparable to those achieved with danazol therapy.[16,21,28]

Other Hormonal Therapy

Oral contraceptives may be used to induce a "pseudopregnancy" and amenorrhea. Although the original studies were performed in the late 1950s with high-dose estrogen, present-day low-estrogen combination pills are generally used. Since amenorrhea is the desired result, patients are given the amount of estrogen needed to produce amenorrhea, although the lowest possible dose should be used on a continuous rather than intermittent basis. The reproductive system responds to the initiation of this therapy as it would to pregnancy, with a resulting increase in vascularity and edema in the endometrium and thus in endometriotic lesions. This initial growth phase may be associated with a worsening of symptoms[30]; large ovarian endometriomas may rupture, causing acute abdomen that requires surgical intervention.[4] Oral contraceptives have numerous side effects, including

weight gain, breast tenderness, nausea, irritability, depression, edema, and hypertension. As a result, as many as 41% of women discontinue therapy.[13] Although oral contraceptives can relieve the symptoms of endometriosis, there is no evidence that they have an effect on the lesions themselves.

Treatment with progesterone alone has also been successful, primarily in the form of medroxyprogesterone.[13,30] Megestrol acetate has also been used successfully to treat the symptoms of endometriosis.[31] This approach is appropriate only for women who have completed childbearing, however, because the time to resumption of normal ovarian function after cessation of therapy may be extremely long (up to 1 year or more). Side effects include abnormal bleeding (breakthrough bleeding in 23% and spotting in 26% of patients) as well as mood changes, depression, and irritability.[30] As with oral contraceptives, progestins relieve pain but have no proven effect on the endometriotic lesions themselves. Nevertheless, progestins may prove to be useful in combination with GnRH agonists. In preliminary studies, they have been found to diminish hot flushes and may help prevent bone loss during GnRH therapy.[32,33]

Surgical Therapy

In cases involving acute rupture of a large endometrioma, ureteral obstruction, large bowel dysfunction, or adnexal masses larger than 8 cm in diameter, surgical therapy is indicated. In other cases, the decision to choose surgical rather than pharmacologic therapy, or to opt for a combination of both, should be based on the patient's age, severity of disease, and desire to maintain childbearing capacity. If laparoscopy is performed to confirm the diagnosis of endometriosis before the initiation of therapy, it would be appropriate to remove some tissue for biopsy and to cauterize obvious lesions during the procedure.

Laparoscopic techniques have become increasingly sophisticated during the last 10 years. Laparoscopic surgery can be performed with electrocautery or with one of a variety of lasers developed for this procedure.[34] An advantage of laparoscopy is that the surgical wound is much smaller than with laparotomy. The time required for the procedure and postoperative recovery is shorter, morbidity and mortality are lower, and the procedure itself overall is less expensive. It is also possible, via the laparoscope, to lyse adhesions, obtain tissue for biopsy, remove small lesions, and cauterize other lesions.

Definitive surgery involves total abdominal hysterectomy, bilateral oophorectomy, and removal of all visible endometriosis. This is reserved for patients with advanced disease who have failed medical therapy and conservative surgery, and for whom fertility is not important. For some women 20 to 40 years of age with advanced disease, hysterectomy with preservation of the ovaries may be appropriate if they have completed childbearing. Other surgical procedures include presacral neurotomy or resection of the ureterosacral ligaments in patients with persistent midline pain such as dysmenorrhea or dyspareunia. However, few patients present with only midline pain. Futhermore, there are some risks associated with cutting vital structures adjacent to these ligaments, and no well-controlled studies have convincingly demonstrated the value of these procedures.[35]

Conclusions

While much remains to be learned about endometriosis, recent advances in pharmacologic and surgical management offer effective and safe treatment for many women, while preserving childbearing potential. Minimally invasive surgery by laparoscopy and monthly intramuscular injections of the GnRH agonist leuprolide acetate are representative of these advances, both of which reduce the morbidity and overall cost of therapy while preserving a high level of function. Until more is learned about the etiology of endometriosis and effective preventive strategies are developed, accurate diagnosis and prompt initiation of therapy offer patients the best hope of reducing the morbidity caused by this common and often debilitating disorder.

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