Endometriosis for the Colorectal Surgeon

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ABSTRACT

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. Although the exact pathophysiology is unclear, endometriosis is a well-known cause of pelvic pain and infertility in reproductive-aged women. Endometriosis can have extrapelvic manifestations relevant for colorectal surgeons to appreciate, such as cyclic constipation, diarrhea, hematochezia, and dyschezia. The treatment of endometriosis involves a combination of medical and surgical interventions where close collaboration between the gynecologist and colorectal surgeon can help achieve prolonged periods of symptom remission.

KEYWORDS: Endometriosis, pelvic pain, reproductive-aged women, infertility

Objectives: On completion of this article, the reader should be able to summarize the different medical and surgical treatment options for endometriosis and appreciate risk factors and symptoms that would put a woman at risk for having underlying endometriosis.

Initially described by von Rokitansky in 1860, endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity.¹ These ectopic endometrial implants are most commonly found in the pelvis, including the ovaries, pelvic peritoneum, uterosacral ligaments, anterior and posterior cul-de-sacs, uterus, and fallopian tubes.^{2,3} However, endometriosis can be found nearly anywhere in the body. Less common sites of involvement include the cervix, bladder, bowel, and pleural and pericardial cavities.^{4,5} Endometriosis can be associated with many distressing and debilitating symptoms and is chiefly found in reproductive-aged women. The disease is responsible for more than 100,000 hysterectomies each year and the annual health care costs attributable to endometriosis exceeds \$1 billion in the United States alone.⁶ Despite extensive investigation endometriosis remains an enigmatic disease with considerable controversy regarding its incidence, pathogenesis, association with infertility, and optimal treatment.

EPIDEMIOLOGY

The prevalence of endometriosis is difficult to quantify, as women may be asymptomatic or suffer varying degrees of pelvic pain. Sangi-Haghpeykar and Poindexter identified endometriosis in 1 to 7% of asymptomatic women undergoing laparoscopic tubal ligation.⁷ This range may approximate the prevalence in the general population. Because of its association with infertility and pelvic pain, endometriosis is notably more prevalent in this subpopulation of women. The disease was prospectively identified in 38.5% of infertile women compared with 5.2% of fertile women.⁸ Among women with pelvic pain, the prevalence of endometriosis ranges from ~40 to 50%.⁹ Nulliparity, early menarche, late menopause, and frequent and prolonged menstrual cycles increase a woman's risk for endometriosis; multiple births and extended periods of lactation appear to be protective.¹⁰ Missmer and colleagues also report the prevalence of endometriosis to be higher in Caucasian women compared with Black and Asian populations.¹¹

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PATHOPHYSIOLOGY

The definitive pathogenic mechanisms of endometriosis are unknown; however, several theories have been proposed. Three leading historical hypotheses include retrograde menstruation, coelomic metaplasia, and lymphovascular spread. More modern theories explore the cause and effect relationship between abnormal endometrium and dysfunctional immune response. The development of endometriosis is an intricate and complex pathogenic process and likely an individualized combination of the aforementioned theories.

Retrograde Menstruation

In 1927 Sampson suggested endometrial tissue shed during menstruation refluxed through the fallopian tubes with subsequent implantation into the peritoneal cavity.¹² These new peritoneal implants invade the mesothelium and develop a blood supply, which allows for persistent survival and growth.⁵ As mentioned above, endometriosis is commonly found in sites contiguous with the fallopian tubes and surrounding areas within the pelvis. Supporting evidence for retrograde menstruation is demonstrated in the observation that women with genital outflow tract obstructions have a higher incidence of endometriosis.¹³ Barbieri found endometriosis was also more common in women with stenosis of the cervical os.¹⁴ However, Bokor and colleagues found the quantity of endometrial cells found in peritoneal fluid to be low during all phases of a woman's cycle, including menstruation.¹⁵ Hence, it is evident that other factors must contribute to the development of endometriosis.

Coelomic Metaplasia

The theory of retrograde menstruation also fails to explain the presence of endometriosis in the absence of menstruation. Endometriosis has been found in premenarchal and postmenopausal women, as well as in men who underwent orchiectomy for prostate cancer and were treated with estrogen.^{16,17} The müllerian ducts and subsequently the female reproductive tract are derived from coelomic epithelium during embryologic development. The coelomic metaplasia theory postulates that the parietal peritoneum contains pluripotent cells that retain the ability to differentiate into endometrial tissue.¹⁸ In vivo and in vitro studies have demonstrated the development of endometriotic lesions from metaplasia of human ovarian surface epithelium.¹⁹ This phenomenon may explain the pathogenesis for the development of ovarian endometriosis. Conversely, there are other tissues derived from coelomic epithelium in which endometriosis is not found.

Lymphovascular Spread

Endometriosis in locations outside of the pelvis, such as the lung, pericardium, or retroperitoneal space, can be explained by dissemination of endometrial cells via lymphatic channels and the vascular system. Endometriosis found involving only retroperitoneal structures in the pelvis without intraperitoneal involvement supports the theory of lymphatic spread.²⁰ Further, endometriotic lesions were identified in incidentally removed lymph nodes in 33% of women with endometriosis.²¹ Still, the propensity of these theories to cause endometriosis in some women but not in others has led investigators to explore additional hypotheses.

Immune Response

The role of the immune system in endometriosis is best described by Braun and Dmowski who view endometriosis as arising from abnormal endometrial cells, which chronically stimulate the immune system, leading to its dysregulation and ultimately the vast spectrum of physiologic changes that are characteristic of the disease.²²

Several studies demonstrate that endometrial cells from women with endometriosis are functionally distinct from endometrial cells of normal women. For example, the expression of estrogen and progesterone receptors is prolonged and distorted in the endometrial cells of women with endometriosis, which may confer a growth advantage in that subset of cells.²³ Additionally, endometrial tissue of women with endometriosis is more resistant to spontaneous apoptosis than that of women without the disease.²⁴

The survival of these abnormal cells is thought to be further enhanced by an altered immune response. An increased number of macrophages are found in the peritoneal fluid of women with endometriosis.²⁵ These macrophages are also found to have a stimulatory effect on endometrial tissue versus the macrophages of women without endometriosis that have a suppressive effect.²² Natural killer (NK) cells, which have cytotoxic activity against foreign cells, are reduced in number in the peritoneal fluid of women with endometriosis.²⁶ Oosterlynck also documented that NK cells of women with endometriosis have decreased cytotoxicity.²⁷

More recent immunologic studies in women with endometriosis have focused on cytokines, which are involved in the signaling of other immune cells. Numerous cytokines, including interleukin-1 β (IL-1 β), IL-6, IL-8, tumor necrosis factor- α (TNF- α), and RANTES (regulated on activation, normal T cell expressed and secreted) are elevated in women with endometriosis.²⁸⁻³¹ Bedaiwy and colleagues found it was possible to discriminate between patients with endometriosis and those without by measuring serum concentrations of IL-6 and TNF- α . IL-8 directly stimulates the proliferation of endometrial cells suggesting it may also play a role in

the pathogenesis of endometriosis.³² RANTES, a cytokine with potent chemo attractant activity for monocytes, is not only elevated in women with endometriosis, but the levels have been found to correlate with the severity of disease.³¹

A survey of the U.S. Endometriosis Association provided evidence that women with endometriosis have a higher prevalence of other autoimmune disorders, such as hypothyroidism, fibromyalgia, allergies, and asthma, when compared with the general population.³³ This lends additional support to the theory of altered immunity in the development of endometriosis.

RISK FACTORS

Familial and Genetic Predisposition

Several studies have demonstrated a familial predisposition to endometriosis. An investigation by Simpson and colleagues reported a 6.9% occurrence rate in first-degree female relatives of women with endometriosis compared with 1% for the non-blood-related control group.³⁴ Similarly, Matalliotakis et al found that first-degree relatives of women with endometriosis have a 10-fold increased risk for endometriosis. Further, patients with a positive family history are more likely to exhibit severe manifestations of endometriosis than those without, 26 versus 12%, respectively.³⁵ A strong concordance among monozygotic twins has also been observed.³⁶

PATIENT SYMPTOMS

Pain

For centuries clinicians have appreciated the many different clinical presentations of endometriosis. Some patients may present with the classic symptoms of pelvic pain and infertility, while others are asymptomatic. The correlation between severity of symptoms and extent of disease is also inconsistent. For example, Fedele and colleagues found no relationship between the anatomic stage of endometriosis and the patient's perception of frequency or severity of pain symptoms.³⁷ Conversely, pelvic pain has been demonstrated to be more common and severe in women with deep infiltrating endometriotic implants.⁵ The underlying mechanism of pain is unclear, but the release of inflammatory cytokines and prostaglandins by ectopic endometrial tissue has been implicated. More recent studies suggest the growth of a nerve supply into endometrial tissue, which can influence the activity of neurons throughout the central nervous system.³⁸

PELVIC MANIFESTATIONS

The pelvic pain of endometriosis varies greatly and may be cyclic or chronic.³⁹ Pain associated with endometrio-

sis is characteristically secondary dysmenorrhea and/or dyspareunia. Secondary dysmenorrhea typically begins 1 to 2 days prior to the onset of menses, and unlike primary dysmenorrhea, the pain can last many days after the cessation of menstrual flow. Cramer and associates found a higher incidence of endometriosis in individuals who exhibited more severe symptoms of dysmenorrhea.⁴⁰ The dyspareunia associated with endometriosis appears to be related to the immobility of pelvic organs and tension on diseased uterosacral ligaments during intercourse.^{41,42}

EXTRAPELVIC MANIFESTATIONS

Less common than dysmenorrhea and dyspareunia are symptoms resulting from endometriosis involving the gastrointestinal and urinary tracts. Cyclic dysuria, urinary frequency, and hematuria concurrent with negative urine cultures suggest bladder endometriosis.⁴³ A rare but serious consequence of urinary tract endometriosis is ureteral obstruction.⁴⁴ Dyschezia is typically present when endometriosis involves the rectosigmoid colon. Cyclic abdominal pain, constipation, diarrhea, and hematochezia are other symptoms suggesting bowel endometriosis.⁴⁵ Very rarely, extensive endometriotic lesions may result in bowel obstruction.⁴⁶ It is difficult to differentiate the symptoms associated with inflammatory disorders of the bowel, such as inflammatory bowel disease or ulcerative colitis, with those of endometriosis. The cyclic nature of symptoms is suggestive; however, the diagnosis of gastrointestinal endometriosis still requires a high index of suspicion by the clinician.

DIFFERENTIAL DIAGNOSIS

The symptoms of endometriosis are nonspecific and many of its clinical features are also present in a wide variety of other gynecologic and nongynecologic disorders. Examples of gynecologic disorders that may mimic endometriosis include pelvic inflammatory disease, ovarian cysts, and adenomyosis. Interstitial cystitis, irritable bowel syndrome, diverticulitis, and musculoskeletal disorders are nongynecologic impersonators. These other potential diagnoses should be considered before surgical exploration for suspected endometriosis.

DIAGNOSIS ALGORITHM

Physical Examination

Physical examination for endometriosis is most diagnostically sensitive when performed during menstruation, as this is the time of maximal swelling and tenderness.⁴⁷ The disease produces tenderness of the pelvic structures and scarring that restricts movement of pelvic organs. Visual inspection of the vagina and cervix are often unremarkable, although occasionally bluish-red

endometriotic lesions may be found in the posterior fornix. A rectovaginal exam may reveal uterosacral nodularity, a fixed, retroverted uterus, or tenderness in the posterior cul-de-sac or rectovaginal septum.

Laboratory Evaluation

Numerous serum biomarkers have been studied as possible noninvasive diagnostic tests for endometriosis. Most extensively investigated is cancer antigen 125 (CA 125), a glycoprotein expressed on the cell surface of some derivatives of embryonic coelomic epithelium. Early on, Pittaway and colleagues reported that 80% of women with pelvic pain and endometriosis had an elevated CA 125, compared with only 6% of patients with pelvic pain without endometriosis.⁴⁸ An additional investigation showed CA 125 to be most reliable in detecting advanced stage disease with a poor sensitivity for detecting mild endometriosis.⁴⁹ Many other conditions have been associated with elevated CA 125, including adenomyosis, pelvic inflammatory disease, uterine fibroids, ovarian cancer, pancreatitis, liver disease, and inflammatory bowel syndrome. Even with new assays the low sensitivity of CA 125 limits its practicality as a diagnostic tool for endometriosis.⁵⁰ Cancer antigen 19-9 (CA 19-9) is another glycoprotein shown to positively correlate with the severity of endometriosis.⁵¹

Imaging

Transvaginal ultrasound (TVUS) is a cost-effective imaging modality for the evaluation of women with pelvic pain. Endometriotic foci identified by TVUS are characteristically hypoechoic.⁵² Moore and colleagues systematically reviewed available data regarding the accuracy of TVUS in the diagnosis of endometriosis and found this technique to be most useful in differentiating endometriomas from other adnexal masses.⁵³ TVUS modalities have proved to be suboptimal in visualizing superficial endometriosis or adhesions.

Magnetic resonance imaging (MRI) is emerging as another accepted diagnostic tool for endometriosis; however, cost limits the routine use of MRI. Typically, endometriotic lesions demonstrate hyperintensity on T1-weighted images and hypointensity on T2-weighted images.⁵² MRI has an accuracy of 94% for deep infiltrating endometriosis compared with 78% for TVUS.⁵⁴ Preoperative evaluation with MRI to guide the surgical approach appears to be appropriate to identify the exact location and extent of lesions when there is a high clinical suspicion for deep endometriosis.

Double-contrast barium enema (DCBE) is another imaging modality used primarily for the identification of colonic involvement in endometriosis. In a prospective trial, DCBE was found to be more accurate in the identification of bowel endometriosis than MRI,

87% and 75%, respectively.⁵⁵ However, when compared with transrectal endoscopic ultrasonography (Tr ESU), Tr ESU proved to have a higher sensitivity (96%) and specificity (100%) than DCBE.⁵⁶

Surgical

Direct laparoscopic visualization and histologic confirmation remains the gold standard for diagnosing endometriosis. Visually, endometriotic lesions have a multitude of appearances, including powder burns, red, blue-black, yellow, white, clear vesicular and peritoneal windows. More extensive disease can lead to the formation of adhesions and cysts. The histologic diagnosis is confirmed by the presence of endometrial glands, stroma, fibrosis, and hemosiderin-laden macrophages.⁵⁷

Classification

Several classification systems have been developed for staging endometriosis by anatomic location and severity of disease. Recently revised in 1996 by The American Society for Reproductive Medicine (ASRM), the most commonly used system assigns a point-score based on the location, width, and depth of endometrial implants, and the presence and severity of adhesive disease by location, thickness, and points of attachment.⁵⁸ The revisions to the classification in 1996 focused primarily to record the progress of disease in fertility patients and predict pregnancy success following treatment of endometriosis. To date there is little data to support the correlation of scoring to pregnancy rates. A separate classification system exists for patients with pelvic pain.⁵⁹ The ASRM system has not been found to correlate well with patient's perceived severity of pelvic pain, thus its clinical application remains limited, except perhaps for providing a standard approach for reporting operative findings.⁶⁰

TREATMENT

Despite extensive research, there remains a paucity of definitive, evidence-based literature regarding the most effective treatment methods for endometriosis. Primary goals of initial treatment are usually directed toward the relief of pain symptoms and promotion of fertility. Long-term therapy is focused at preventing progression and recurrence of the disease. Treatment options for endometriosis include medical, surgical, or a combination of both.

Medical Management

A variety of medications have been shown to reduce pain-associated endometriosis including nonsteroidal antiinflammatory drugs (NSAIDs), oral contraceptives,

gonadotropin-releasing hormone (GnRH) agonists, danazol, and progestins.

Historically, danazol was one of the first medications approved for the treatment of endometriosis in the 1970s. This drug is a synthetic androgen, and through suppression of the luteinizing hormone surge produces a hypoestrogenic, hyperandrogenic state resulting in atrophic changes in endometrial tissue.⁶¹ The prominent androgenic side effects of danazol including acne, weight gain, hirsutism, adverse lipid profiles, and voice deepening significantly limit its routine use.

NSAIDs are the most commonly used first-line treatment for women with pelvic pain and endometriosis. Their mechanism of action relates to the inhibition of prostaglandins, which in part, are responsible for the pain and inflammation associated with endometriosis. Another option for patients with pain is combination oral contraceptive pills (COCs).⁶² Ovarian suppression with COCs induces decidualization and atrophy of endometrial tissue. A double-blind, randomized, placebo-controlled trial demonstrated a significant improvement in dysmenorrhea associated with endometriosis with COC use compared with placebo.⁶³ The study also found a significant decrease in the size of endometriomas with COCs. Adverse effects associated with COCs primarily relate to the increased risk of hypertension and deep-vein thrombosis with use of exogenous estrogen.

If symptoms are unresponsive or contradictions exist to COCs alternative therapies may be appropriate. Progestins antagonize estrogenic effects on the endometrium resulting in decidualization and endometrial atrophy. Various compounds include oral progestins, depot medroxyprogesterone acetate (DMPA), and the levonorgestrel-releasing device (LNG-IUD). A randomized controlled trial by Telimaa and colleagues showed oral MPA significantly reduced endometriosis-associated pelvic pain and resolution of peritoneal implants occurred in 60% of patients at second-look laparoscopy, compared with 18% in the placebo group.⁶⁴ Side effects of DMPA include weight gain, irregular bleeding and prolonged period to resumption of ovulation.

Recent observational trials have shown the device to effectively improve symptoms of endometriosis.⁶⁵ Petta et al found the LNG-IUD to be equally as effective as GnRH agonist therapy without provoking hypoestrogenic side effects.⁶⁶ LNG-IUD requires only one medical intervention every 5 years, and accordingly may be an attractive management option for women with endometriosis.

Gonadotropin releasing hormone (GnRH) agonist therapy results in pituitary desensitization and loss of ovarian steroidogenesis, thus producing a medical menopausal state.⁶⁷ The side effects of GnRH agonist therapy are hot flushes, vaginal dryness, insomnia and decrease in bone mineral density. Therapy is usually

limited to a 6-month course, particularly because of the potential effects on bone density. To minimize bone loss and vasomotor symptoms, GnRH agonists and add-back regimens using progestins alone or low dose progestin/estrogen combination pills will minimize both bone loss and vasomotor symptoms allowing for a longer duration of therapy without sacrificing efficacy.

Surgical Management

Endometriosis is a complex disease with immense variation and the choice between medical management and surgical therapy must be individualized. There is little evidence to support one treatment strategy over another. In general, surgical therapy is reserved for women who have failed medical management or those with known moderate to severe disease and worsening symptoms such as acute cases of ureteral obstruction, bowel obstruction, or rupture of large endometriomas. The primary goals of surgical management are to remove all visible lesions of endometriosis and restore normal anatomy. Some of the challenges to successful surgical treatment lie in the surgeon's ability to recognize and remove endometrial implants. Histologic analysis often shows incomplete resection of implants in even experienced surgeons.⁶⁸

A variety of operative techniques are utilized including resection, laser vaporization, coagulation, and electrocautery. Severe cases of endometriosis can be technically challenging due to obliteration of dissection planes from dense disease and associated adhesions. Lesions can often be found infiltrating or adjacent to the bowel, bladder, or ureter where coordination between the gynecologist and colorectal surgeon will ensure optimal surgical debulking of disease.

Definitive surgical management, including hysterectomy, bilateral oophorectomy, and removal of all visible disease, offers the most prompt, effective, and long-term relief of pain from endometriosis. According to a study at Johns Hopkins Hospital, women who had ovarian conservation at the time of hysterectomy were six times more likely to have a recurrence of chronic pelvic pain and eight times more likely to require additional surgery, compared with those who underwent bilateral oophorectomy at the time of hysterectomy.⁶⁹ More recently, Modugno and colleagues have found women with endometriosis to be at increased risk of developing ovarian cancer.⁷⁰ Thus, hysterectomy alone has little role in the modern management of chronic pelvic pain associated with endometriosis in women who have completed childbearing.

Laparoscopy versus Laparotomy

Operative laparoscopy is the surgical treatment of choice for pelvic pain related to endometriosis. It confers many

advantages over laparotomy, such as treatment at the time of diagnosis, decreased postoperative morbidity and mortality, shorter recovery time, and reduction in adhesion formation.⁷¹ Laparoscopy also provides optimal visualization of the posterior cul-de-sac and allows for magnification of peritoneal surfaces to aid in identification of subtle disease. One randomized controlled trial found laparoscopy with fulguration of endometrial implants and uterosacral nerve ablation provided symptom relief in 62.5% of women, compared with 22.6% of diagnostic laparoscopy alone.⁷² Laparotomy is most useful in cases of dense pelvic adhesions and large endometriomas. Deep invasion of the rectovaginal septum, extensive bowel, or urinary tract involvement and infiltration near the uterine vessels may also be optimally approached via laparotomy.

Denervation Procedures

Occasionally denervation procedures, such as presacral neurectomy or uterine nerve ablation, may be performed in cases of severe midline pain, deep dyspareunia, and dysmenorrhea. The presacral neurectomy (PSN) is one option for the treatment of midline pelvic pain associated with endometriosis. PSN is a technically challenging procedure and vascular complications can be severe, thus it is used sparingly in carefully selected patients who only complain of midline pain. Early reports of the laparoscopic uterosacral nerve ablation (LUNA) were promising for the treatment of endometriosis-associated pelvic pain; however, findings have not been reproduced in randomized controlled trials. Thus, based on the current available evidence, the routine use of LUNA in women with endometriosis is not supported.

Combination Medical and Surgical Therapy

Comprehensive management of endometriosis involves a combination of medical and surgical interventions. Intuitively, some clinicians postulate preoperative disease suppression with hormonal agents will decrease vascularity and allow for easier tissue dissection, thereby decreasing operative time and postoperative adhesion formation. However, a clinical trial of patients undergoing laparoscopy for endometrioma excision found no reduction in operating time or recurrence rate of disease at 1 year for those treated preoperatively with a 3-month course of GnRH agonist compared with those with no preoperative treatment.⁷³ On the other hand, if a patient does not desire to attempt immediate conception, postoperative medical therapy may prolong the duration of pain relief and reduce the risk of adhesion recurrence.^{74,75} A randomized controlled trial by Vercellini et al reported in patients undergoing operative laparoscopy secondary to endometriosis, moderate or severe dysmenorrhea recurred in 10% of patients treated

postoperatively with LNG-IUD versus 45% of those expectantly managed.⁷⁶

PROGNOSIS

Endometriosis is a surgical disease. Long-term outcomes appear poor, with the probability of recurrent pain ranging from 20 to 40% and the need for additional surgical procedures between 15 and 20%.⁷⁷ Other investigators further stratify recurrence rates and quote the estimated risk to be 21.5% at 2 years and 40 to 50% at 5 years.⁷⁸ Close collaboration between the gynecologist and colorectal surgeon is critical to achieving aggressive surgical debulking of endometriosis affected tissue and prolonging periods of symptom remission.

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