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Endometriosis: The Etiology and Recommended Treatment

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Abstract

Endometriosis is a gynecological condition that occurs in women between the ages of 15 and 49 years, in which endometrial cells grow outside the uterus. Normally, endometrial cells form the endometrium and respond to hormones throughout the menstrual cycle, but when endometrial cells are located outside the endometrium, painful bleeding and other side effects may occur. Treatment of endometriosis is usually symptomatic relief, including the use of oral contraceptives and other hormone replacement options, as well as non-steroidal anti-inflammatory drugs. To ensure that patients receive the appropriate treatment for this condition, pharmacists should be able to recognize the signs and symptoms of endometriosis and refer patients to physicians. Pharmacists also play a key role in patient education about the medications and surgical treatments to manage the symptoms and pain associated with endometriosis.

Introduction

Endometriosis is a gynecological condition in which endometrial cells grow outside the uterus. This condition commonly affects women between the ages of 15 and 49 years. The endometrial cells typically form the endometrium, or lining of the uterus, and respond to hormones, such as estrogen, throughout the menstrual cycle. These hormones stimulate menstrual bleeding after a woman's typical menstrual cycle.¹ When endometrial cells are located outside the uterus, they respond to hormones in the same manner leading to bleeding which can be extremely painful.² However, some women with endometriosis may be asymptomatic and these cases often go undiagnosed. Other cases of endometriosis may go undiagnosed due to inappropriate diagnosis as a different disease or conditions such as premenstrual syndrome (PMS). Endometriosis commonly occurs on the outside surface of the uterus, the vagina, fallopian tubes, rectum, behind the cervix and on the ovaries.³ The growth, swelling, and breakdown of endometrial tissue outside the uterus can cause lesions which can permanently scar. Awareness of the risks, causes and symptoms of endometriosis may lead to a more effective treatment outcome and, in turn, improve the patient's quality of life.

Risk Factors and Causes of Endometriosis

The growth of endometriosis is dependent upon hormones, especially estrogen. However, hormones are not responsible for the proliferation of the endometrial cells outside the uterus. One possible cause of endometriosis is retrograde menstruation, a condition where uterine lining is present in the fallopian tubes and potentially the abdomen, rather than the vaginal cavity. Although many women experience retrograde menstruation, most women avoid endometriosis with the help of their immune system. Women affected by endometriosis may have abnormal functioning of their immune

system, in which the immune system allows endometrial cells to begin growing on other organs. The lymphatic system may carry endometrial cells to other organs as well which results in growth further from the uterus.³

Endometriosis can occur in any woman of child bearing age. However, some women are at a higher risk of developing endometriosis. A major risk factor in developing the disease is the presence of familial history of endometriosis in a primary female relative. An irregular menstruation cycle can also increase a woman's risk of developing endometriosis. A woman who experiences early onset of menstruation before 12 years of age may have an increased risk of developing the condition. The risk of endometriosis also increases for women experiencing menstrual bleeding for more than seven consecutive days. This prolonged bleeding time may be an indication of bleeding from physiologically different areas of the body other than the uterus. If a woman cannot or chooses not to have children, her risk of developing endometriosis increases; pregnancy typically decreases the progression of the condition due to a decreased amount of estrogen.² A woman's uterus may have a physiological defect or abnormal development potentially causing endometriosis to occur.³ There is no single cause or risk factor responsible for the development of endometriosis, but it is important for women to be informed of the potential risks they have for developing the condition.

Symptoms of Endometriosis

Not all women that have endometriosis experience symptoms. However, recognition of the main symptoms of endometriosis is important in early diagnosis of a woman with the disease. The most common symptom of endometriosis is pain and cramping in the pelvic region especially prior to and during menstrual bleeding. Pain may also occur during bowel movements, during urination or as cramping in the lower back. Menstrual bleeding may become heavier than normal. Sexually active women may experience dyspareunia, or pain during sexual intercourse. Endometriosis can lead to infertility and miscarriage. If a woman is having trouble becoming pregnant or carrying a fetus to full term, she may have endometriosis.³ If a woman is experiencing these symptoms, she should schedule an appointment with her doctor to have a pelvic exam.

Pharmacologic Treatment of Endometriosis

There are several strategies for the treatment of endometriosis. Treatment goals include controlling pain, slowing endometrial growth, and restoring or preserving fertility. Treatment options depend on a variety of factors, including severity of symptoms, size and location of growths, the degree of scarring and extent of the disease, if the patient wishes to conceive and at what age.³ The American College of

Obstetricians and Gynecologists updated guidelines in 2010, which detail treatment strategies for each type of patient based on the previously listed factors.⁴ First line agents for the treatment of dysmenorrhea, include non-steroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptives, which are hormone replacement medications that contain both estrogen and progestin. Medroxyprogesterone acetate, danazol and aromatase inhibitors are agents used for noncyclic chronic pelvic pain (defined as pain in the pelvic region lasting more than three months) and as second line treatment for dysmenorrhea. Agents that can be used second or third line for dyspareunia and dysmenorrhea are levonorgestrel intrauterine system and gonadotropin-releasing hormone (GnRH) agonists.⁵

Combined oral contraceptives can be used as a first line treatment with or without NSAIDs for relief of endometriosis related pain in women who are not trying to conceive at the time of treatment. Although they are associated with a 20 to 25 percent failure rate in the treatment of pelvic pain associated with endometriosis, combined oral contraceptives are preferred over danazol or GnRH agonists because they are generally well-tolerated.⁵ Combined oral contraceptives work in relieving this pain by inhibiting ovulation, decreasing gonadotropin levels, and reducing menstrual flow and buildup of the endometrium during the menstrual cycle.⁶ While oral contraceptives can be beneficial when used on a continuous basis to prevent menstruation, the endometrial growth that was decreased throughout treatment tends to reverse when treatment is stopped. This makes oral contraceptives a difficult treatment choice for anyone who wishes to become pregnant, because the patient will have to discontinue the drug before being able to conceive.³

Progestin only products, such as medroxyprogesterone acetate, are also a viable option for the treatment of endometriosis as an alternative to combined oral contraceptives. These drugs work by halting menstruation and the further growth of the endometrium, which will help relieve the signs and symptoms of endometriosis. Although not considered the treatment of choice, other hormonal treatments of endometriosis include GnRH agonists and antagonists. These products can be used to block the production of ovarian-stimulating hormones, leading to lower estrogen levels, which causes the endometrial growths to shrink. GnRH agonists, such as leuprolide and norelgestromin, inhibit luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion, after an initial hormone flare. Continuous administration of GnRH agonists suppresses gonadotropin release through a negative feedback mechanism to the hypothalamus. GnRH antagonists have a more immediate inhibition of FSH and LH secretion. Unlike GnRH agonists, GnRH antagonists work by directly inhibiting FSH and LH release, and do not require a feedback mechanism. Examples of GnRH antagonists include ganirelix and cetrorelix.⁷

Another treatment option for endometriosis is danazol, a testosterone product that works by blocking the production of ovarian-stimulating hormones and therefore preventing menstruation. Danazol has also been shown to suppress the

growth of the endometrium, making it a very effective treatment for endometriosis. However, danazol is not considered first-line due to undesirable side effects including alopecia and acne.⁸

Non-steroidal anti-inflammatory drugs are commonly prescribed as a first-line treatment for women experiencing dysmenorrhea and pain caused by endometriosis.^{5,9} Non-steroidal anti-inflammatory drugs effectively inhibit cyclooxygenase (COX) enzymes, thereby inhibiting the production of prostaglandins, a likely cause of endometriosis-related pain. However, NSAIDs have no effect in decreasing or removing any endometrial deposits.⁹

Recently, it has been noted that the COX enzymes, more specifically the COX-2 isoform, are involved in regulation of cell growth and apoptosis. Activation of the non-steroidal anti-inflammatory growth factor (NAG-1) by NSAIDs effectively decreases cell proliferation and enhances apoptosis in cells, including endometrial cells.^{10,11} A 2008 in vitro study investigated cell proliferation and apoptosis response of endometrial cells to treatment with various concentrations of celecoxib in patients with endometriosis. At dosages of 50, 75 and 100 micromolar (μM), there was a significant effect on cell apoptosis induction versus control, with p values <0.05 , <0.001 , and <0.001 , respectively. At these same concentrations, there was also a significant decrease in cell proliferation versus control, with p values <0.05 , <0.01 , and <0.001 , respectively.¹¹ In addition to its effects on cell proliferation and apoptosis, celecoxib has also been shown to inhibit implantation of endometrial tissue. Like other COX inhibitors, COX-2 inhibitors additionally provide pain relief. The results of these data suggest that selective COX-2 inhibitors are an option for effective treatment, and even prevention, of endometriosis.¹⁰

For the reduction of dysmenorrhea and pain symptoms, NSAIDs must be taken a few days before or on the first day of menses.⁵ Common side effects of NSAIDs include headache, dizziness, drowsiness, nausea, diarrhea, and GI irritation.^{5,9} Selective COX-2 inhibitors have fewer GI effects, but the potential risk for cardiovascular thrombotic disease may be increased.¹⁰

Laparoscopic Procedures

Laparoscopies for the diagnosis and treatment of endometriosis comprise 25 to 35 percent of all laparoscopic procedures yearly. Surgical treatment, such as laparoscopy, is not typically first-line treatment. Indications for this surgery include ineffective pain control or relief with NSAIDs, severe pain that lasts several months, and pain that requires one to miss school/work or requires hospitalization.¹²

Laparoscopy treatment can include: fulguration, ablation, and excision; excision or drainage and ablation; or laparoscopic presacral neurectomy (LPSN) of the tissues and cysts. The latter, LPSN, nerve-pathway interruption, also aids in control of pain by removal of the presacral nerves.⁵ No studies have investigated the therapeutic outcome differences between the laparoscopic procedures, but individual treat-

ments have been investigated for recurrence of endometriosis and pain. In a study comparing laser treatment of endometriosis, including nerve transection, to aspiration of fluid, 20 out of 32 patients and seven of 31 patients, respectively, reported symptom improvement/relief six months after surgery. In the laser group, 90 percent of those who stated relief at six months experienced relief at one year, with only 10 percent (two patients) noting a return of symptoms.¹³

Laparoscopic surgery is often an option chosen by women wishing to conceive. Several systematic reviews have shown an increase in rate of pregnancy, nine to 12 months following surgery in one review, and a five-fold increase in pregnancy rate in another review, after laparoscopic surgery. There is some concern about diminishing ovarian reserve with laparoscopic surgeries, and as a result, in vitro fertilization is recommended for women who have endometriosis after repeated laparoscopic procedures.¹³

Recurrence of endometriosis after laparoscopic surgery is common.^{12,14} Three important factors found to be determinant of repeat surgery were: older age, post-operative pregnancy and symptomatic improvement. Women who experienced pelvic pain rather than fertility problems were more likely to undergo or require another surgery. Location of endometrial tissues and cysts also played a significant role in whether or not another surgery would be required.¹⁴

The risks associated with laparoscopic surgery are not different than risks associated with any other surgical procedure, including anesthesia risk, infection, hemorrhage, potential damage to internal organs and new adhesions.⁵

Pharmacist's Role

Endometriosis is a disease that affects many women among various age groups, so it is important that pharmacists understand the pathology of the disease and also treatment options and goals. While pharmacists cannot directly diagnose endometriosis, it is important to recognize signs and symptoms of the disease so that they can refer patients that present with questions about these symptoms to their physician. There are many different treatment options for this disease so it is necessary for pharmacists to collaborate with patients and physicians to help the patient receive the best individualized treatment. Pharmacists should be able to educate the patients on potential treatment options and also be able to explain possible side effects and risks associated with each treatment. Even for those patients who choose surgery as a treatment, pharmacists have a role in helping patients with their post-surgery management of medications.

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