Endometriosis update

Susan P. Willman, MD*

Introduction

Endometriosis is a medical condition found primarily in women of reproductive age. It can cause infertility and a wide range of pain symptoms. Typically, dysmenorrhea occurs one or two days before menses begins, then continues for several days. In some cases, the pain can last the entire cycle. Some women experience pain during intercourse or bowel movements, along with diarrhea, constipation and urinary symptoms. The pain can feel like pressure or cramping and might be characterized as sharp or radiating. Often, over-the-counter medications only offer partial relief.

The condition derives its name from the endometrium or the inner lining of the uterus. The endometrium has a functional layer, consisting of both glandular epithelium and stroma (supportive tissue). During each menstrual cycle, this layer grows in response to estrogen before being sloughed off with menstruation. In endometriosis, endometrial glands and stroma implant outside the uterus, usually in the abdominal cavity.

Endometriosis is most commonly found on the ovaries. The next most common sites include the peritoneum below the uterus near the rectum (posterior cul de sac), between the bladder and the uterus (anterior cul de sac), behind the ovaries (posterior ovarian fossa) and around the fallopian tubes.[1,2] Endometriosis can also be found on the bowel, bladder, appendix and in distant locations such as the umbilicus and the lungs.[1-3]

Endometriosis might be simplistically characterized as a condition where normal cells are found in an abnormal location. However, it is a more complicated picture. Aside from their ability to implant, endometrial cells can also grow in size, invade and destroy normal tissue and form their own blood vessels (angiogenesis) to promote growth further.[4] Endometriosis is not well understood, and its exact cause has remained elusive. This has hampered efforts to achieve effective long-term treatments.

Incidence

Knowing the precise prevalence of this condition is difficult because symptoms do not correlate directly with disease presence or severity. In addition, there are multiple causes of pain and infertility in women, and a definitive diagnosis typically requires a direct view (e.g., laparoscopy). The reported incidence of endometriosis will vary depending on what population is scrutinized.

For example, a 1982 study documented endometriosis in 2% of fertile women undergoing laparoscopy for elective tubal ligation compared with 21% of infertile women undergoing diagnostic laparoscopy.[5] If the incidence of endometriosis is focused just on women with symptoms, the chance of endometriosis is higher. When pain is the presenting symptom, the prevalence of endometriosis in published studies ranges from 30 to 80%. When infertility is the symptom, the range is from 9 to 50%.[6]

The risk factors for endometriosis are many. One risk is related to having a higher lifetime number of menstrual cycles. This might be due to early menarche (before age 13), late menopause, short cycles (fewer than 27 days) and few or no pregnancies (i.e., more periods). Some factors are associated with physiological or psychological stress such as cigarette smoking, alcohol use, history of sexual or physical abuse and low body mass index. Endometriosis is more common in Caucasians and in first-degree relatives of those with severe endometriosis, suggesting a genetic component.

Lifestyle factors have also been implicated. Dietary intake data from the Nurses' Health Study II (1989-2001) was correlated with an endometriosis diagnosis. Those women with diets high in trans fats were more likely to be diagnosed with endometriosis while women with diets high in long-chain omega-3 fatty acids had a lower probability of endometriosis.[7] Long-term oral contraceptive use might be protective against severe endometriosis.[3] Given these different associations, the cause of endometriosis does appear to be multifactorial—another reason it has remained a bit of an enigma.

*The creator of this publication is an independent author and is not an employee or agent of Walgreens or AllianceRx Walgreens Prime. Additional information about the author may be viewed on page 6 of this publication.

Diagnosis

A history of painful menses, pain with intercourse and infertility are suggestive of endometriosis. Pain upon pelvic exam, a retroverted uterus fixed in position and thickening or nodularity of the uterosacral ligaments on the rectovaginal exam are presumptive but not diagnostic. A definitive diagnosis requires further confirmation.

As endometriosis lesions are often small with a density similar to surrounding tissues, pelvic ultrasound and MRI are not reliable for diagnosis. Laparoscopy remains the primary mode of definitive diagnosis of endometriosis.[8] However, sometimes a biopsy of a lesion in an unusual location (e.g., the umbilicus, vagina or lung) confirms endometriosis.

The extent of endometriosis can vary, with lesions ranging in size from 1 mm to > 10 cm.[6] Their appearance can be quite varied: red, white, purple, puckering, bleb-like, adhesions, pseudo-pockets. Endometriosis can be superficially located on the peritoneum it can involve the ovaries or can be deeply infiltrating. Deeply infiltrating endometriosis is defined as being greater than 5 mm below the peritoneum, typically solid and frequently in the rectal area or near the ureter.[3] Adhesions are often associated with more extensive disease.

Endometriosis involving an ovary creates a cyst filled with old blood. This endometrioma, or chocolate cyst, has a characteristic appearance on ultrasound. When an endometrioma is present on one ovary, there is a 30% risk of involvement in the other ovary.[1-3]

Stages of endometriosis

To encourage effective communication of the severity of disease between physicians and to promote standardization of studies, the American Society for Reproductive Medicine (ASRM) developed a staging system for endometriosis in 1996.[9] At laparoscopy, each lesion of endometriosis is given a numerical rating based on size and density. The cumulative score of all lesions is the stage:[3-6,8-9]

- Stage I is minimal and consists typically of a limited number of superficial implants and no significant adhesions.
- Stage II is mild, with superficial implants whose surface area adds to less than 5 cm, and no significant adhesions.
- Stage III is moderate, with superficial implants and deeply infiltrating disease, often with adhesions.
- Stage IV is severe and has more implants with extensive adhesions and, often, endometriomas.

While the stage does not always correlate with pain symptoms, women who are asymptomatic are more likely to have Stage I-II endometriosis. Staging is helpful for infertility counseling, as the more advanced stages of endometriosis have a greater negative effect on fertility.

Pathogenesis

At the 1927 meeting of the American Gynecological Society, Dr. John A. Sampson presented his observation of 293 cases of endometriosis over five years. He postulated that endometriosis originated from the flow of menstrual blood from the uterus through the tubes and into the abdominal cavity (retrograde menstruation). His observations have been memorialized as “Sampson’s Theory.”[10]

Sampson made several hallmark observations:

- Retrograde menstruation actually occurs. (Present-day estimates are that 70-90% of women have retrograde menses.)[3]
- Endometrial cells are present in menstrual blood.
- Endometrial cells can implant and grow.
- There is a relationship between varying hormone levels and the disease process.

All these observations have stood the test of time. They have been supported by the observation that women with an obstruction of the normal outflow of menses (e.g., birth defects of the uterus or vagina that prevent vaginal flow of menses) have a greater risk of endometriosis. However, Sampson’s theory did not explain endometriosis completely.

In particular, why is endometriosis sometimes seen in prebubertal girls, men (though rare) and women who have had a hysterectomy? Why do some women get endometriosis and others do not? The fact that endometriosis is seen fertile women without pain symptoms suggests that mild forms of endometriosis could be a normal variant or a transient condition. Endometriosis typically regresses in about one-third of affected women, progresses in another one-third, and remains the same in about 40% of cases.[11] How can these variable presentations be explained?

A second theory of mesothelial cell metaplasia, postulated in 1942, suggested some explanations.[12] In the abdominal cavity, mesothelial cells comprise one layer of the peritoneum. Metaplasia is the reversible transformation of one cell type to another cell type. The mesothelial cell metaplasia theory proposed that peritoneal cells or stem cells or endometrial cells could become endometriosis when triggered by a stimulus.

Supporting this theory is the finding that endometriosis lesions have altered physiology when compared with endometrial cells. For example, like the endometrium, endometriosis cells have estrogen and progesterone receptors. Estrogen stimulates endometriosis while progesterone slows its growth. However, unlike the endometrium, endometriosis lesions produce estrogen locally through high levels of aromatase activity while exhibiting progesterone resistance.[12]

The modern genetic/epigenetic theory better explains the variability of the condition. According to this view, endometriosis begins either with early microscopic implants of endometrial cells or with a progenitor stem cell that has an inherited or acquired genetic alteration predisposing it to metaplasia.[12] A hereditary genetic variant is stable and passed through generations. An acquired defect might be a recent change in the DNA sequence that occurred during regular cell division in the creation of new daughter cells. This may or may not be a permanent inheritable change.

The transformation of a cell to endometriosis could be triggered by local or environmental stress. The combination of a genetic variant plus an external trigger could have a cumulative effect of changing the cell. Multiple events and multiple genetic variants could explain the variability of the disease.[12]

Applying this theory, some cells with a genetic variant and no external triggers might see a regression of the disease. Likewise, more insults and more genetic variants could lead to more severe disease.[12] The environmental stimuli for changes in cell function and physiology are speculative. Possible triggers include pelvic infection, debris or an altered microbiome or oxidative stress induced by degraded red blood cells, iron and degraded endometrial cells in menstrual reflux.[12,13]

Endometriosis is an inflammatory condition that could be viewed as a stress response. The increased overall volume of peritoneal fluid of the pelvic and abdominal cavity suggest inflammation. Macrophages in the fluid appear in high numbers and in a more activated state. These mobile white blood cells are part of the natural immune defense, and their increased presence and activity allude to an inflammatory process. There is also an increase in many inflammatory by-products generating an extensive list of associated toxic factors such as cytokines, prostaglandins, proteases, growth factors such as vascular epithelial growth factor and angiogenic factors.[12,13]

Infertility

Endometriosis can decrease fertility through many mechanisms. Extensive adhesions can cause deformed anatomy, such as tubes and ovaries that become adherent to the pelvic side wall of the uterus. Adhesions can also impair a fallopian tube's ability to pick up the egg. The unfavorable milieu of inflammation or oxidative stress might impair fertilization by sperm and affect egg quality.[6,13] A short luteal phase, low progesterone levels, and unruptured follicle syndrome have also been linked to endometriosis.

Lower ovarian reserve is a well-documented risk for women with more advanced endometriosis. A cross-sectional study showed women with endometriomas have a lower antral count and lower levels of the antimullerian hormone (AMH). In an age-control matched study, AMH levels in 40 women with endometriomas larger than 3 cm were compared with AMH levels in 40 women without endometriosis. Over six months, the endometrioma group had a greater decline in AMH levels than the control group.[14]

Some investigators suggest women with endometriosis might have impaired implantation. However, this implication does not hold up to the observations of normal implantation rates in women with endometriosis who are treated with egg donation. Due to the progressive nature of the condition, women with endometriosis are encouraged to pursue family building as early as possible. In women with good ovarian reserve, in vitro fertilization (IVF) can be an effective treatment option for fertility when other measures are ineffective. IVF with oocyte or embryo freezing are becoming viable options as well.

Pain

There is no relationship between the extent of endometriosis and the severity of symptoms. Some women with severe endometriosis have no pain while some with the minimal disease report severe pain. Pain is thought to come from the inflammatory nature of the disease.

Other sources of pain might include bleeding from implants and nerve irritation with deep invasion. It has been observed that severe pain is more likely with deeply invasive disease. In addition, many other diseases have symptoms that overlap with endometriosis. These include pelvic inflammation, irritable bowel syndrome, interstitial cystitis, and pelvic floor dysfunction.[8]

Other health risks

Women with endometriosis face an increased risk of pregnancy complications such as miscarriage, ectopic pregnancy, placenta previa, peripartum hemorrhage, cesarean delivery, preterm birth, and low birth weight babies.[3,15] Research also suggests endometriosis is

associated with a low but increased risk of ovarian cancer and a higher risk of cardiovascular disease.[3] The presence of systemic chronic inflammation and increased oxidative stress might be the link between endometriosis and other health problems. Yet undescribed genetic risks might also be to blame.

Treatment

Endometriosis treatment can be surgical, medical or, more often, a combination of the two. Unfortunately, no studies have directly compared surgery with medical treatment.[4] While medical suppression has been shown to be effective for treating pain, it has not been shown to help with fertility. Surgical treatment can be helpful for both pain and infertility. However, it is highly desirable to avoid multiple surgical procedures.

Surgical treatment

As laparoscopy is needed to confirm the diagnosis, surgical treatment often is a first intervention. Surgical removal of endometriosis can be effective in reducing pain, more so for moderate to severe endometriosis than for minimal or mild disease.[8] Surgery can also help treat infertility, but the recurrence risk is high, within five years.

For endometriomas larger than 1 cm, surgery is often recommended because medical treatment is ineffective. However, the surgical excision of an endometrioma carries the risk that normal ovarian tissue might be destroyed in the process, decreasing an already compromised ovarian reserve.[6] A systemic review of 237 patients, demonstrated a drop in AMH levels after surgical excision of an endometrioma.[14] Choosing between surgery and IVF for patients with endometriomas and infertility remains a controversial topic.

Hysterectomy with removal of both fallopian tubes and ovaries is the most definitive treatment for refractory pain, but it is a last resort. It should be offered when childbearing is no longer desired, and all other measures have failed. Estrogen hormone replacement after complete hysterectomy can be associated with recurrent disease. Adding progesterone to the hormone replacement regimen after surgical menopause supports a lower risk of recurrence.[8] While surgery followed by medical treatment can delay the return of pain, long-term management should focus on medical treatment.[8]

Medical treatment

Estrogen stimulates the growth of endometriosis, so the paradigm for medical treatment has been to suppress or reduce estrogen production. As a consequence, menstruation is suppressed and so is ovulation, forgoing active conception for treatment of pain. This is often a difficult choice for patients.[3]

Studies evaluating medical treatment are few and difficult to perform. There is a large placebo effect, even with endometriosis-related pain. Because most medical treatment induces amenorrhea, it is difficult to conduct a blinded study comparing a drug with placebo.

Established medical treatments

Pain medication

Nonsteroidal anti-inflammatory medications are the mainstay treatment of pain. A Cochrane review showed insufficient data to conclude efficacy, but it is the only option that leaves open the possibility of conception.[8]

Contraceptive treatment

Oral contraceptives (OCPs) can be administered either cyclically or continuously. Continuous OCPs suppress menses and are more effective for menstrual pain control. In one study, continuous OCP use was more effective than cyclic use for pain relief -post-surgery.[8]

Continuous progestogens, including medroxyprogesterone acetate, norethindrone, levonorgestrel, and dienogest, will also treat the pain of endometriosis. Progestogens might result in atrophy of endometriotic lesions by suppressing enzymes that support the growth of endometriosis (matrix metalloproteinases). Progestins might also interfere with angiogenesis. Progestogen treatment is equally effective as other medical treatment.[8] More recently, the progesterone IUD has been found to be effective for treating the pain of endometriosis. It also might help with deeply invasive disease.[8]

Hormonal modulation

Danazol is one of the oldest proven medications for endometriosis. It is not used as often today because of the high incidence of side effects, including hirsutism, acne, weight gain, and deepening of the voice. It is a derivative of testosterone with a mixed-steroid activity. It works by inhibiting luteinizing hormone (LH) surge (and ovulation) and steroid production. Using the lowest dose to induce amenorrhea and using the vaginal application instead of oral dosing can minimize side effects.[8]

Gonadotropin-releasing hormone (GnRH) agonists are used extensively for endometriosis. They work by suppressing the pituitary release of follicle-stimulating hormone and LH and inducing a low-estrogen state and amenorrhea. Side effects include hot flushes, vaginal dryness, and bone loss. Add-back therapy of low estrogen and progesterone addresses concerns for decreases in bone density. The theory is that

low doses of estrogen can treat side effects without stimulating the growth of endometriosis.[8, 16]

There has been recent interest in pretreating IVF patients with GnRH agonists. However, only one clinical trial out of three showed higher live birth rates. The potential fertility benefits of GnRH agonists need further study.[4]

Investigational medical treatments

Central sensitization
Central sensitization is an approach based on a theory that peripheral pain signals are amplified in the brain. Tricyclic antidepressants and antiepileptics can dampen those signals. Trigger-point injections might also decrease the release of pain signals.[4]

Hormonal modulators
Pituitary suppression is more rapid and direct with GnRH antagonists, which are being developed for endometriosis treatment. An oral medication, elagolix, has been shown to be effective, safe and well-tolerated in Phase 1 and Phase 2 clinical trials.[4] In another study, elagolix was shown to provide pain control similar to medroxyprogesterone acetate. The weekly injection cetrorelix was also found to be effective for disease regression.[4] Because of the resulting low estrogen levels; both can have the same side effects as GnRH agonists.

Aromatase inhibitors
The aromatase enzyme converts testosterone into estradiol. It is found in endometriosis cells and may help endometriosis implants grow. Aromatase inhibitors such as letrozole or anastrozole can block this enzyme and help treat endometriosis. Animal studies have shown that this category of medications can eradicate endometriosis implants. These medications are not currently FDA-approved for the treatment of endometriosis, but off-label use has become commonplace. They are used continuously and only in combination with other medications that suppress ovulation, including OCPs, progestins and GnRH analogs.[4,8]

Selective progesterone receptor modulators

Of interest has been whether or not long-acting progesterone antagonists could help with endometriosis. Mifepristone is a progesterone antagonist used for medical abortions. It has been developed in the form of an implant and has been studied rats with induced endometriosis.[4] Ulipristal might also have potential as treatments for endometriosis.[4] Ulipristal is currently used for emergency contraception in the United States and treatment of fibroids in Europe and Canada, but has not yet been studied for endometriosis treatment.

Selective estrogen receptor modulators
Synthetic hormones that compete with and inhibit estrogen activity are also of interest for treating endometriosis. Raloxifene, which is used to treat menopausal osteoporosis, was first tested in mice but failed human trials due to significant pain. Newer medications in this category are under development.[4]

Nonhormonal treatment
Nonhormonal treatment holds the possibility of treating endometriosis while allowing for conception. However, these medications must be free of any risk for birth defects.

Immunomodulators, which regulate the immune response, have theoretical benefit for treating the inflammatory nature of endometriosis. Etanercept, which blocks tumor necrosis factor, has been shown to decrease endometriosis in rats. Many other immunomodulating agents are undergoing investigation.[4]

Research is also focused on growth factor inhibitors and angiogenesis inhibitors, though no medication of this type has yet shown clinical efficacy in treating endometriosis. In this category, statins have been studied in mice and in cultured human cells. The dopaminergic agonist cabergoline has also been studied in mice, as it decreases vascular endothelial growth factor and could be a future treatment option.[4]

Conclusion

Endometriosis is a complex disease with varied facets and presentations. While it can be a clinical challenge to diagnose and treat, new research holds promise for more effective treatments. A greater understanding of unique individual characteristics of the disease could enable a personalized medical approach for each patient.[4]

A better understanding of the genetic role in endometriosis improves the possibility of medical intervention tailored to genetic variants of the disease. One could envision that clinicians could study a biopsy of an endometriosis lesion for its genetic and metabolic profile and develop a medical treatment plan to offset the disease process. In the interim, early diagnosis and intervention are critical to decreasing the negative effects on fertility and quality of life.

For more information, visit Walgreens.com/hcp

About the author

Susan P. Willman, MD, has specialized in reproductive endocrinology and infertility since 1992. She has been a primary investigator in IVF clinical studies regarding embryo selection through time-lapse imaging and preimplantation genetic testing.

Always interested in advances in the field, Dr. Willman received an ASRM award for her video presentation on the use of sonography as an adjuvant to operative hysteroscopy. She also holds expertise in robotic laparoscopic surgery specializing in myomectomy and surgical treatment of endometriosis for fertility.

Dr. Willman was with the Reproductive Science Center of the San Francisco Bay Area for nearly two decades before moving to her current affiliation with the Contra Costa Regional Medical Center. She received her medical degree cum laude from St. Louis University School of Medicine and completed her residency in obstetrics and gynecology at the University of Texas Southwestern, where she received an award for her work in diabetes in pregnancy. She completed a fellowship in reproductive endocrinology at the University of California San Francisco.

Dr. Willman belongs to the ASRM, the European Society for Human Reproduction and Embryology, the Preimplantation Genetic Diagnosis International Society and the American Association of Gynecologic Laparoscopy. She attends medical meetings both in the United States and abroad, recognizing that the field of medicine is global and that different viewpoints from different societies enhance the field of medicine.

References

1. Audebert A, Petousis S, Margioula-Siarkou C, Ravanos K, Prapas N, Prapas Y. Anatomic distribution of endometriosis: A reappraisal based on series of 1101 patients. Eur J Obstet Gynecol Reprod Biol. 2018;230:36. Epub 2018 Sep 5.
2. Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. Obstet Gynecol. Mar; 1986; 67(3):335-8.
3. Schenken RS, Barberi RL, Ekler K. Endometriosis: pathogenesis, clinical features, and diagnosis. UpToDate Web site. https://www.uptodate.com/contents/endometriosis. Updated Jan 2019. Accessed March 14, 2019.
4. Bedaiwy MA, Alfaraj S, Yong P, Casper R. New developments in the medical treatment of endometriosis. *Fertil Steril*. 2017;107(3):555-565.
5. Strathy JH, Molgaard CA, Coulam CB, Melonton LJ III. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. *Fertil Steril*. 1982; 38(6):667-672.
6. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. *Fertil Steril*. 2012;98(3):591-598.
7. Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, Barbieri RL, Willett WC, Hankinson SE. A prospective study of dietary fat consumption and endometriosis risk. Hum Reprod. June 2010;25(6):15235.
8. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertil Steril*. 2014;101(4): 927-935.
9. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril*. 1997;67(5)817-821. https://www.fertstert.org/article/S0015-0282(97)81391-X/pdf. Accessed March 14, 2019.
10. Sampson JA. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol*. 1927;14:422-429.
11. Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril*. 2004;82(4):878-884.
12. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Gomel V, Martin DC. Pathogenesis of endometriosis: the genetic/epigenetic theory. *Fertil Steril*. 2019;111(2):327-340.
13. Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. *Fertil Steril*. 2016;106(5):1101-1017.
14. Kasapoglu I, Ata B, Uyaniklar O, et al. Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study. *Fertil Steril*. 2018;110(1):122-127.
15. Vigano P, Corti L, Berlanda N. Beyond infertility: obstetrical and postpartum complications associated with endometriosis and adenomyosis. *Fertil Steril*. 2015;104(4):802-812.
16. Bedaiwy MA, Allaire C, Alfaraj S. Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy. *Fertil Steri*l. 2017; 107(3):537-548.

Walgreens | allianceRx Walgreens + PRIME