Endometriosis [1]

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Endometriosis is a medical condition that involves abnormal growths of tissue resembling the endometrium [3], which is the tissue that normally lines the inside of the uterus [4]. Those growths, called endometrial lesions, typically form outside the uterus [4], but can spread to other reproductive organs such as ovaries and fallopian tubes [5]. Endometrial lesions swell and bleed during menstruation [6], which can cause painful and heavy menstruation [6], as well as infertility [7]. As of 2021, there is no cure for endometriosis [8], although medical therapies such as birth control [9] pills and GnRH analogues can treat the painful symptoms of endometriosis [8]. More than eleven percent of women between the ages fifteen and forty-four in the US have endometriosis [8], which can often decrease a woman's quality of life due to painful symptoms and impair her reproductive potential.

Endometriosis is a condition that may cause changes in the normal menstrual cycle, a process that prepares the female body for the possibility of pregnancy [10]. The first part of the menstrual cycle is menstruation [6], which happens when the endometrium [3] is thick and filled with blood. During menstruation [6], the uterus [4] sheds the thick endometrium [3], and it leaves the body through the vagina [11]. After menstruation [6], one of the next steps of the menstrual cycle is a process called ovulation [12] that starts at the ovaries, which are reproductive organs that release hormones [13] and store egg [14] cells. Ovulation occurs when one of the two ovaries releases an egg [14] cell. The egg [14] cell goes through the fallopian tube, which attaches to the ovary [15] to the uterus [4], where the egg [14] cell can meet a sperm [16] cell that fertilizes the egg [14] cell. The fertilized egg [17] cell later attaches itself to the endometrium [3] inside the uterus [4] and pregnancy [10] starts. If a sperm [16] cell does not fertilize the egg [14] cell, then the menstrual cycle begins again.

Some historians credit the German physician Karl Freiherr von Rokitansky with discovering endometriosis [8] when he published some of the earliest identifications of the condition in 1860. Using microscopes to examine tissue samples taken from patients’ bodies, Rokitansky found endometrial cells growing in unusual parts of the body, such as the myometrium, the middle tissue layer of the uterus [4], and the ovaries. He described those findings in an article, called “Über Uterus- und Ovarial-Sarkome” (On Neoplasias of the Uterine Glands in Uterine and Ovarian Sarcomas). There, Rokitansky put forth the identification of endometrial cells growing in other regions of the body as some of the first diagnostic criteria for endometriosis [8]. According to the Ronald Batt, who has written about the history of endometriosis [8], medical professionals still base definitions of endometriosis [8] today on the criteria that Rokitansky first put forth. However, the researchers Ivo Brosens and Giuseppe Benagiano, who have written extensively about endometriosis [8] and other reproductive health issues, point out that Rokitansky called the lesions that he observed sarcomas, a term associated with malignant growths, or growths that spread uncontrollably. Brosens and Benagiano suggest that Rokitansky misunderstood the lesions he observed and should consequently not be credited with discovering endometriosis [8], though historians like Batt disagree.

In 1920, the physician Thomas Cullen presented a more complete clinical picture of endometriosis [8], which has led scholars such as Brosens and Benagiano to credit him with the discovery of the condition over Rokitansky. Cullen published a series of detailed diagrams and descriptions in the journal Surgery that visually represented endometrial growths that he had observed in different areas of the pelvic region. Cullen’s descriptions were some of the first to not only describe growths outside of the uterus [4] but infer that they were of endometrial origin without suggesting that the growths were malignant as Rokitansky seemed to.

Though researchers like Rokitansky and Cullen had described endometriosis [8], few had proposed a mechanism by which the condition could come about before John Albertson Sampson in 1927. While performing surgeries in the abdominal areas of his patients in the 1920s, Sampson noticed that the endometrial lesions growing in abnormal places bled at the same time as his patients were menstruating, which showed him that the lesions were of endometrial origin. In 1927, Sampson presented those findings at the American Gynecological Society meeting in Hot Springs, Virginia. There, he also introduced the theory of what he called retrograde menstruation [6] to explain how endometrial lesions develop outside the uterus [4]. According to that theory, endometrial lesions develop when menstrual blood containing endometrial cells flows backward through the fallopian tubes [5], rather than through the vagina [11], and into the pelvic cavity. The endometrial cells then attach to reproductive organs and grow into lesions outside those organs. Sampson articulated his theory of retrograde menstruation [6] in his 1927 paper called “Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation,” in The American Journal of Pathology, where he was one of the first to formally use the term endometriosis [8] to describe the condition.

Then in 1932, researcher Luther L. Hill Jr. published an article in The American Journal of Surgery where he was one of the first to describe and distinguish between a wide range of endometrial lesions and symptoms associated with endometriosis [8]. In a study of 135 patients who received surgery to examine possible endometriosis [8], many reported painful menstruation [10]. Hill Jr. found that endometrial lesions appeared differently among the patients. Specifically, nineteen percent of the patients had
endometrial lesions that were small and only recognizable under a microscope \[18\], while twenty-six percent of patients had endometrial lesions that were, as Hill Jr. describes, fairly extensive. Additionally, Hill Jr. reports varying descriptions of endometrial lesions, referring to three cases that had ruptured, chocolate-colored small fluid-filled growths, called cysts. Also in his article, Hill Jr. discusses the symptoms associated with endometriosis \[8\] that he observed. For instance, he writes that twenty-two percent of the patients reported menorrhagia, or heavy menstrual bleeding, and twenty-six percent of the patients reported dysmenorrhea, or painful menstruation \[8\]. Although Hill Jr. states that the patients presented such a wide range of endometrial lesions and symptoms, that he could not offer a single salient description of endometriosis \[8\], his findings provided more insight into the many ways endometriosis \[8\] may physically manifest in the body.

In the 1950s, as researchers continued to improve their understanding of endometriosis \[8\], they developed better treatment options for patients with the condition. At the time, a hysterectomy \[19\], or surgical removal of the uterus \[6\], was the only option to treat endometriosis \[8\]. However, some physicians attempted to recommend other, non-surgical options. For instance, in 1953, physician Józef Vincent Meigs wrote in the journal Obstetrics & Gynecology that he advised patients with endometriosis \[8\] to become pregnant early and frequently, as endometrial lesions stop growing during pregnancy \[18\] because the menstrual cycle stops. Then, in 1958, the physician Robert W. Kistner proposed that a more practical treatment would be reproducing the effects of pregnancy \[10\] on the body by using hormones \[13\], which can reduce the growth of endometrial lesions without a woman having to actually become pregnant. That same year, the US Food and Drug Administration \[20\], or the FDA, approved the use of one of the first birth control \[9\] pills called Enovid \[21\] to treat menstrual disorders like endometriosis \[8\]. Birth control pills manipulate hormones \[13\], such as estrogen \[22\] and progesterone \[23\], to control and suppress the menstrual cycle, which stops endometrial lesions from swelling and bleeding. That helps relieve painful symptoms of endometriosis \[8\], as swelling and bleeding of endometrial lesions often causes people to experience pelvic pain during menstruation \[8\]. As of 2021, birth control \[9\] pills continue to be a common treatment for symptoms of endometriosis \[8\].

Another common treatment for symptoms of endometriosis \[8\] as of 2021 is the use of gonadotropin \[24\]-releasing hormone \[25\] analogues, or GnRH analogues. GnRH is a hormone \[25\] that the hypothalamus in the brain produces and sends to the pituitary gland \[20\], which signals the ovaries to produce estrogen \[22\] that controls the menstrual cycle. GnRH analogues inhibit the production of estrogen \[22\], which can suppress the menstrual cycle and consequently alleviate symptoms of endometriosis \[8\]. One example of a GnRH analogue is called leuprolide, which the FDA first approved for medical use in 1985. However, GnRH analogues like leuprolide can cause the female body to enter a temporary menopause. That is because the suppression of hormone \[22\] production causes symptoms of menopause, including night sweats, hot flashes, the absence of menstruation \[8\], and mood swings. While GnRH analogues and birth control \[9\] pills are common treatments for the symptoms of endometriosis \[8\], they do not cure the condition and can cause women to experience other side effects.

Throughout the twentieth century, physicians also developed better methods of diagnosing endometriosis \[8\]. According to Brosens and Benagiano, laparoscopy started to become a popular gynecological tool during the 1940s. During a laparoscopy, a surgeon makes small incisions on the abdomen to insert a tool, called a laparoscope, that has a small camera to view the internal organs. By 1970, gynecologists in Europe and the US officially declared laparoscopy to be the preferred tool to diagnose endometriosis \[8\] because it allows the most accurate observation of endometrial lesions.

To diagnose endometriosis \[8\] using laparoscopy, the surgeon uses the laparoscope to search for endometrial lesions outside of the uterus \[4\]. The appearance of endometriosis \[8\] can vary, ranging from small lesions to large, dark-colored lesions. Cysts can also form in more severe cases of endometriosis \[8\], where blood has accumulated over time. In conjunction with laparoscopy, physicians also use histological confirmation, a process of viewing lesions that physicians extract from the body under a microscope \[18\], to confirm endometriosis \[8\]. That helps physicians look at the cellular composition of the lesion and compare it to that of the normal endometrium \[18\], as lesions may be indicative of other inflammatory changes in the pelvis. As of 2021, physicians continue to diagnose endometriosis \[8\] with a combination of laparoscopy and histological confirmation, as well as use laparoscopy to remove painful lesions as a method of treating endometriosis \[8\].

Physicians can diagnose patients with endometriosis \[8\] differently according to the stage of their condition. The American Society for Reproductive Medicine divides cases of endometriosis \[8\] into four different stages that physicians can diagnose depending on the severity of lesions. On a scale from I to IV, the organization \[27\] called those stages minimal, mild, moderate, and severe, respectively. In severe cases of endometriosis \[8\], lesions can grow on other reproductive organs, the bladder, and part of the bowel, as well as remote areas of the body such as the lungs and kidneys. The different areas and organs on which the endometrium \[3\] grows can swell and bleed, because the abnormal endometrial growths continue to proliferate and shed during menstruation \[6\], like the normal endometrium \[3\] does. Those lesions can elicit painful physical responses in a woman’s body, especially during menstruation \[8\].

In addition to causing painful side effects, researchers have also associated the presence of endometrial lesions with infertility \[7\], though how endometriosis \[8\] causes infertility \[7\] remains unclear. According to Carlo Bulletti, who researches reproductive science at the University of Bologna \[28\] in Bologna, Italy, and his colleagues, as many as thirty to fifty percent of women with endometriosis \[8\] experience infertility \[7\]. In more severe cases of endometriosis \[8\], endometrial lesions may distort the pelvic anatomy, obstructing the passage of the egg \[14\] cell through the fallopian tube during ovulation \[12\] or both the egg \[14\] and sperm \[16\] during fertilization \[29\]. Researchers still lack evidence of other ways that endometriosis \[8\] might cause infertility \[7\] outside of
when endometrial lesions distort the pelvic anatomy. Some have suggested that endometriosis \(^8\) may impair fertilization \(^{29}\) and implantation \(^{30}\), as well as inhibit embryonic development.

Some researchers have also posited that endometriosis \(^8\) may cause infertility \(^7\) because it increases the amount of peritoneal fluid and macrophages in a woman's body. Peritoneal fluid is a liquid that lubricates the tissue that lines the abdominal and pelvic cavities, and macrophages are cells that recognize and respond to infections in the body, often causing inflammation. Because the abnormal growth of the endometrium \(^{3}\) has inflammatory effects on the female body, researchers suspect that women with endometriosis \(^8\) might have increased peritoneal fluid volume and a higher concentration of macrophages as the presence of those materials causes inflammation. In 1994, researchers T. Shakil and S.A. Whitehead found that an increased number of macrophages in the peritoneal fluid may impair ovulation \(^{12}\). That is because the researchers found that a high number of macrophages and its inflammatory effects inhibit hormone \(^{25}\) production in the ovaries, which may have an impact on fertility. However, the correlation between endometriosis \(^8\) and infertility \(^7\) remains elusive, as there are many different explanations and ways in which endometriosis \(^8\) may cause infertility \(^7\).

Because infertility \(^7\) is a common symptom of endometriosis \(^8\), women who are diagnosed with endometriosis \(^8\) and wish to become pregnant may choose to receive a fertility treatment to specifically address infertility \(^7\). One example of a fertility treatment is a medication called clomiphene citrate \(^{31}\). That medication helps stimulate ovulation \(^{13}\) in women who do not regularly ovulate. Another example of a fertility treatment is in vitro fertilization \(^{32}\), or IVF, which is a procedure in which asperm \(^{16}\) cell fertilizes an egg \(^{14}\) cell outside of the body, in a petri dish. According to the physician Matthew Latham Macer and researcher Hugh S. Taylor, who both investigate or work with IVF in the context of women's health, IVF is the most effective treatment of endometriosis \(^8\)-associated infertility \(^7\).

Despite the existence of such treatments, because endometriosis \(^8\) impacts fertility as well as mental health, education, and work, researchers often associate it with a decreased quality of life. Studies have shown associations between endometriosis \(^8\) and decreased quality of life, including a higher prevalence of depression and anxiety and an increased risk of missing educational and professional opportunities. For example, in 2019, physician Maryam Moradi and colleagues surveyed women with endometriosis \(^8\) and developed a questionnaire that physicians can use to better understand the psychological and social impacts of the condition. The research team found that endometriosis \(^8\) has negative impacts on women’s quality of life, affecting their relationships, educational and employment opportunities, and social lives.

Also, endometriosis \(^8\) is often associated with lengthy diagnostic delays, which may perpetuate negative mental health, education, and work outcomes. For example, women may wait as long as seven years to be diagnosed with endometriosis \(^8\). That diagnostic delay may come about because of several reasons, including difficulty distinguishing between normal and abnormal symptoms of menstruation \(^8\). For instance, because women often learn and expect cramps to be a normal symptom of menstruation \(^8\), they may be unaware that abnormally painful cramps may be indicative of endometriosis \(^8\). According to Mindy Christianson, a physician and associate professor at the Johns Hopkins University School of Medicine \(^{20}\) in Baltimore, Maryland, cramps are normal during menstruation \(^8\), but debilitating cramps that keep people from completing their normal everyday activities may be due to endometriosis \(^8\).

In 2018, to address the quality of life and well-being of women with endometriosis \(^8\), New York state senators Sue Serino and Monica R. Martinez, and assembly member Linda Rosenthal introduced legislation that would provide educational materials about endometriosis \(^8\) and other menstrual cycle-related conditions in New York school districts and health care clinics. According to Serino, Martinez, and Rosenthal, the goal of the legislation was to improve knowledge of endometriosis \(^8\) and get rid of stigma associated with menstruation \(^8\). Educational materials may influence those with undiagnosed endometriosis \(^8\) to seek health care interventions and obtain early diagnosis and treatment for the condition. In November 2019, New York governor Andrew Cuomo signed the legislation into law.

Although laparoscopy and histological confirmation is the preferred way to diagnose endometriosis \(^8\), as of 2021, researchers are searching for non-surgical tools to diagnose endometriosis \(^8\). For example, as of 2021, researcher Christine Metz, who helps lead the Research OutSmarts Endometriosis, or ROSE, study at the Feinstein Institutes for Medical Research in Manhasset, New York, compares the cellular composition of menstrual blood from women with and without endometriosis \(^8\). Through its investigation, the ROSE study found what they call major differences between cells of patients with and without endometriosis \(^8\). One of those differences is that cells that support the functions of endometrial tissue, called stromal cells, have an impaired ability to decidualize, or transform into specialized cells, in patients with endometriosis \(^8\). Typically, hormones \(^{13}\) signal stromal cells to decidualize into cells that can support and provide nourishment for a developing embryo, which is a fertilize egg \(^{14}\) cell that attaches to the endometrium \(^3\) during pregnancy \(^{10}\) and may eventually develop into a fetus \(^{34}\). However, the ROSE study’s finding may indicate that because the stromal cells are less able to decidualize in cases of endometriosis \(^8\), the endometrium \(^5\) may not provide an adequate environment for fetal development in people with the condition. That could have implications for the relationship between endometriosis \(^8\) and fertility. Further, according to the ROSE study, those findings may help develop a quicker, non-surgical method to diagnose endometriosis \(^8\) that only requires looking at markers of endometriosis \(^8\) in patients’ cells.

Even as researchers have had evidence of endometriosis \(^8\) for centuries, awareness of the condition has only increased in
recent decades. In 1980, Mary Lou Ballweg and Carolyn Keith established the Endometriosis Association, which claims to be one of the oldest organizations in the world to support women with the condition. In 1993, the Endometriosis Association started Endometriosis Awareness Month, which takes place during March. A yellow ribbon symbolizes Endometriosis Awareness. As of 2021, other organizations exist to increase awareness of endometriosis, support people with the condition, and help find a cure. Among other organizations leading endometriosis research and awareness efforts are the Endometriosis Research Center and World Endometriosis Research Foundation. Those organizations are focused on research to better understand the physical, environmental, and genetic factors that influence endometriosis and its effect on women’s overall health. Such research has the potential to benefit millions of people diagnosed with the condition.

Sources


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