What is endometriosis?

If you are of childbearing age and have a uterus, you are at risk of endometriosis. Endometriosis is the development of endothelium-like lesions on the outside of the uterus and is a common cause of infertility in women[1]. Many sufferers report chronic fatigue as well as persistent pelvic pain. They don't sleep well, they can't void their bowels, and sex becomes painful. For others, it is a silent condition that is only discovered when they see their doctor about infertility. Still, others remain entirely unaware that they have the disease. What is going on?

In a healthy woman, a lining called the endometrium forms inside her uterus each month. Its purpose is to house and feed a recently conceived fetus. If no pregnancy occurs, this lining is shed during her next period.

What are the symptoms of endometriosis?

This chronic condition can potentially affect these women from puberty to menopause. Endometriosis occurs when endometrial-like cells grow inside the pelvic cavity[2]. Most often, this happens on the outside wall of the uterus and, less commonly, in other areas within the pelvis. How does this occur, and what can be done about it?

In many ways, endometriosis can be considered a syndrome rather than a distinct disease. There are a range of symptoms linked to the presence of these growths. Furthermore, the number and size of these lesions are unrelated to the severity of the symptoms. Not all women are infertile and can experience varying degrees of pain. Could it be possible that there is more than one cause of endometriosis?

How is endometriosis diagnosed?

Current medical guidelines in Canada[3], the USA[4], and the UK[5] recommend conservative approaches to diagnosing endometriosis. Medical imaging, such as ultrasound and MRI, along with a physical exam, is the preferred approach for most doctors[6]. However, in some cases, imaging may overlook the growth. Laparoscopic, or keyhole surgery, can detect these lesions in the pelvic cavity. Despite being a minimally invasive technique, this surgery has its complications. Wouldn't it be wonderful to have a simple blood test for diagnosing the disease? While several promising blood markers have been identified in the laboratory, they don't detect the disease in everyone[7].

A more promising approach is to use small molecules, called miRNA, for early detection of the disease. These miRNAs are found throughout the body and help regulate cell growth[8] by regulating the life cycle of cells. When they detect an abnormality, their numbers significantly increase, summoning the appropriate immunity authorities. They are involved in several other conditions, such as diabetes and autoimmune diseases. There are a large number of these molecules associated with endometriosis[9,10,11,12,13,14,15,16,17]. Could one of these signals alert doctors to endometriosis before it can form?

On the imaging front, there is also much promise. Maraciclatide is a small molecule capable of binding to actively growing bodies such as cancerous growths and endometrial lesions. Once labelled with safe amounts of radioactivity, the lesions can be seen via scintigraphy, a scan similar to an X-ray image. This fascinating technique is covered in more detail here.

What are the treatments for endometriosis?

There is currently no cure for endometriosis. Fortunately, many of the symptoms can be controlled with oral contraceptives, also known as 'The Pill' or other hormonal therapies[1]. Other drugs that have shown efficacy include gonadotropin-releasing hormone inhibitors and aromatase inhibitors[18]. All these strategies aim to reduce estrogen levels in the body and lower endometrial buildup in the uterus. In more advanced cases, keyhole surgery can remove the growth.

Unfortunately, these strategies are not a solution for those looking to conceive. Other approaches must be used to reduce inflammation and manage pain - using anti-inflammatories such as Ibuprofen. Clinical trials have shown that vitamin supplementation, especially vitamins C, D and E, can also be effective[19,20]. These vitamins have an anti-inflammatory effect on the body, which may explain their effectiveness here. A healthy diet, rich in antioxidants, can also help with symptoms[21].

Who is at risk of endometriosis?

Several studies have identified some risk factors that people with endometriosis share. However, not all of these factors are present in every sufferer.

- Family history
- High levels of estrogen
- No previous pregnancies
- Low body weight
- Smoking
- Early onset of puberty
- Short menstrual cycles - less than 27 days
- Heavy menstrual periods - lasting over seven days

What causes endometriosis?

Scientists do not know how endometriosis begins. Several theories have been proposed to explain the condition's clinical events[22]. Unfortunately, none of them can satisfactorily explain all facets of the disease.

A promising start: In 1922, Dr. John Sampson proposed his theory of retrograde menstruation [23]. He suggested that the flow of some endometrial cells during a woman's period could reverse direction and migrate out of the uterus, along the fallopian tubes, and enter the pelvic area[24]. Indeed, this reversed process has subsequently been observed in many healthy women. The problem is that only a tiny fraction of those develop endometriosis. Why could this be? What happens to those endometrial cells in just a small subgroup of women? The pelvic cavity, or peritoneum, is an inhospitable environment for an orphaned endometrial cell. The environment has limited oxygen and nutrients due to a lack of blood supply to the area. Why do these cells implant and grow against the odds?

Or not: Perhaps these growths are not from the endometrium. Perhaps they are embryonic cells left over from the developing fetus that have been transformed into endometrial-like cells by some unidentified factor. This idea is more plausible than it may sound. It was originally proposed as the embryonic rest theory[25]. Here, the cells were descended from the developing female reproductive tract, a structure known as the Mullerian duct. Another theory, coelomic metaplasia, goes further back in development and credits the coelom with its origin[26]. The coelom is the early embryonic body cavity that houses all our internal organs.

These transformed cell theories are plausible but cannot be proven — at least not yet. They might, however, explain exceedingly rare cases of endometriosis found in prepubertal girls[27] and men[28]. Unfortunately, some endometrium-like tissue has been found in far-flung parts of the body[29], including the brain[30]. The brain is not formed from the same part of the embryo. Back to the drawing board?

Could stem cells be the smoking gun?

Fortunately, science progresses, usually in the wake of technology. In 2009[31], undifferentiated stem cells cultured from endometrial tissue provided support for the eighty-year-old theory of retrograde menstruation [32,33]. Stem cells, usually found in bone marrow, can turn into any other cell in the body. Researchers have now identified these cells in endometrial tissue. These would be ideal candidates, given the influence of endometrial cells to turn into endometrial-like growths[34]. Stem cells can survive in harsh environments, such as the pelvic cavity. They would be ideal candidates as the trigger in developing these unwelcome lesions[35]. Could they be the smoking gun? In theory, yes. Research is ongoing in this field to provide conclusive proof[36].

What about contributory factors?

The above theories attempt to explain the origin of endometriosis. What about the environment within the pelvic cavity? Are there external factors that aid in the formation of these lesions? The short answer is yes, probably.

The Immune System: In healthy people, the immune system is tightly controlled. Foreign objects are identified and removed from the body. Conversely, it shouldn't overreact to normal healthy tissue and attack it. In the case of chronic diseases like endometriosis, the immune system can malfunction[37]. Women with endometriosis have an increased inflammatory response in their pelvic cavity[38]. This is likely due to inflammatory components of the immune system being detected in the lesions[39] and failing to remove them. Misfiring of the immune system might explain why a foreign misplaced cell in the pelvic cavity isn't recognised and removed[40]. If some types of immune cells, such as natural killer cells, migrate into the pelvic cavity, they could potentially initiate both the adhesion and stability of early lesions in the hostile peritoneum[2]. They are simply doing their job but are in the wrong place.

Mum and Dad: Endometriosis runs in families. Studies on twins have shown that you have a 50% chance of developing endometriosis if your twin has it[41]. Scientists have combed through thousands of human genomes and identified genes that may be responsible for the more severe forms of the disease[42]. Several additional genes have been discovered linked not only to endometriosis but also to other inflammatory and hormonal diseases[43]. It is important to remember that these preliminary studies have limitations and are not considered convincing medical proof. None of the identified genes conclusively cause endometriosis but are associated with it[44]. These may not be "bad" genes, but they might live in a bad chromosomal neighbourhood. To date, there is no high-quality evidence linking endometriosis with any particular gene or set of genes.

The Environment: We live in an increasingly toxic world, and cases of endometriosis are rising with it. Could environmental factors play a role in the development of the disease[45]? Many environmental pollutants have been observed to disrupt hormonal regulation in women[46]. Air pollutants, in particular, can boost inflammation[47]. These byproducts of manufacturing processes do not degrade quickly and can exist in our environment for decades. Another culprit can be found in plastic bottles - bisphenol A (BPA).

Investigators are investigating dioxins in our environment[48]. Dioxins are produced as byproducts while manufacturing many modern products, such as paint and herbicides. Studies have shown that exposure to these pollutants can increase the risk of endometriosis in monkeys [49]. Many nations have banned these antiquated industrial processes to reduce environmental toxic levels. Unfortunately, dioxins have a half-life of 7-11 years[50] - we may have to coexist with them for decades.

Hope for the future

Endometriosis is a chronic disease with an unknown cause worsened by risk factors that are often beyond a patient's control. However, there is hope. In 2023, doctors at the University of Edinburgh initiated a small clinical trial to treat the symptoms of endometriosis with the anticancer drug dichloroacetate (DCA)[51]. DCA is used in cancer treatment[52], but experiments in test tubes have shown that it could effectively reduce inflammation in endometrial cells. Astonishingly, experiments in mice found that the drug could also reduce the size of lesions[53]. Thirty human volunteers tolerated the drug well, with a few reporting slightly upset stomachs and tingling in the fingers. For the millions of women who are suffering pain "worse than childbirth", it might be a sacrifice they are willing to make.

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