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REVIEW PAPER

Endometriosis as female reproductive system disorder: mechanisms, diagnosis and clinical management

Mahta Bagheri [1], Fateme Zohre-Vand [1], Mahya Hamzeie [2], Babak Arji Roudsari [2,*]

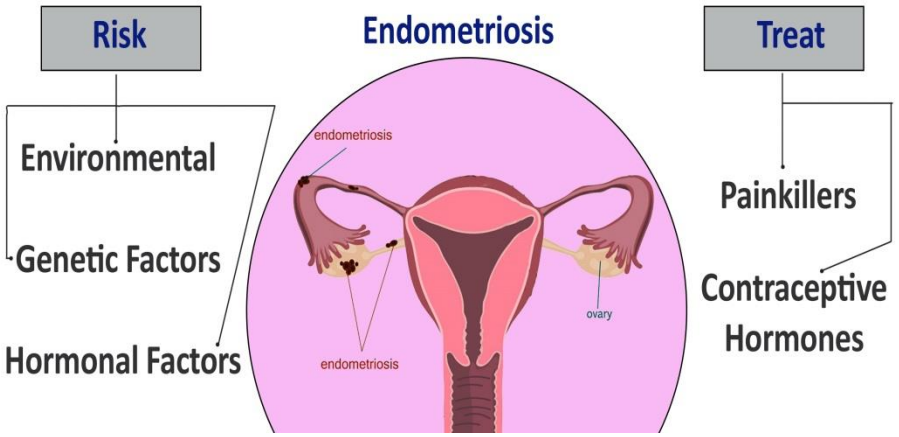
[1] Member of Research Committee, Medical School, Hamedan University of Medical Sciences, Hamedan, Iran

[2] Department of Anatomical Sciences, Medical School, Kermanshah University of Medical Sciences, Kermanshah, Iran

Highlights

- Endometriosis is a chronic and inflammatory gynecological disease that affects 10% of women.
- Various factors such as environmental and genetic factors and hormonal factors can change the endometriosis risk.
- Painkillers and contraceptive hormones can be good ways to treat the endometriosis.

Graphical Abstract



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Abstract

Endometriosis is a gynecological, chronic, and inflammatory disease affecting one in ten women globally. It occurs when tissues similar to the endometrial layer of the uterus grow outside the uterine body leading to inflammation, pain, and infertility. The most common site of endometriotic lesions is the pelvic cavity, especially the ovaries. Thus, at the same time as menstruation, these points initiate bleeding, which results in many difficulties. So far, several mechanisms of endometriosis have been suggested, such as retrograde menstruation, the influence of environmental and genetic factors, and hormonal causes. In some cases, this pathologic condition occurs following pregnancy or pelvic surgery. Disease management also involves the use of painkillers and contraceptive hormones for a relatively long time or even the use of laparoscopy to remove the pathologic lesions. In this review, the mechanisms of endometriosis were discussed, as well as various aspects of the disease in the field of diagnosis and treatment were assessed.

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*Corresponding author: babak.arji@gmail.com (B. Arji Roudsari)

Introduction

Endometriosis is a common, chronic, and benign disorder in women which refers to the growth of endometrial tissue outside the uterus like ovaries, uterosacral ligaments, and the pouch of Douglas (1). Sometimes endometriosis occurs in extra-genital sites, such as diaphragmatic pleural or umbilical lesions (2). Endometriosis affects 20-50% of infertile women and 6-10% of women of reproductive age and 70% of women with chronic pelvic pain (3). It is a hereditary hormone-dependent disease that is associated with inflammation, pelvic pain, and infertility. Endometriosis has an inherited pattern. First-degree relatives of people with endometriosis are 6-9% more likely to develop the disease than normal people. Also, this type of disease comprises 15% of all severe diseases. On the other hand, the prevalence and age of onset of this disease are the same in twin sisters. Researches showed that heredity is considered as 50% of all endometriotic cases, even in women who underwent hysterectomy (4).

There is no definitive cause for the pathophysiology of endometriosis but various risk factors include several genetic and environmental aspects that are effective. Shorter menstrual length, menstruation at young ages, taller height, high body mass index (BMI), and smoking are among the risk factors (5). After the invention of the laparoscopy procedure in the 1970s, endometriotic lesions were safely diagnosed in women with pain and infertility (4). Superficial peritoneal lesions, ovarian endometrioses, and deep infiltrating endometriosis are three well-recognized phenotypes of endometriosis (Figure 1A). Deep infiltrating endometriosis is the most severe type which penetrates to a depth of more than 5 mm beneath the peritoneal surface or as lesions in the muscles of the organs surrounding the uterus. The American Reproductive Medicine Association (ARMA) categorized endometriosis into 3 stages; severity, type, and location of the lesions. Finally, in high grades of endometriosis, surgery is strictly recommended (6).

Although endometriosis is a progressive disease, the lesions, especially deep rectovaginal lesions, showed non-rapid growth. Also, the recurrence rate of the lesions after their complete removal was very low (4). Nonetheless, this disease has many negative consequences on the activities of daily life, personal relationships and sexual function and unfortunately, due to the late diagnosis, women with endometriosis usually have severe pelvic pain for a long time. Also, because this disease is one of the main causes of female infertility, it is an important issue in women's health. Thus, it should be seen as a social health problem, not an individual disorder (7). In this study, we narrate the mechanisms involved in the pathogenesis of endometriosis, its diagnosis and effective treatment strategies.

Possible pathophysiology mechanisms of endometriosis

Among the mechanisms suggested for endometriosis, retrograde menstruation is the most accepted hypothesis, which refers to the condition in which blood from the discharge of the endometrial layer of the uterus returns to the pelvis and fallopian tubes instead of the vaginal canal. In this case, it can implant, develop and sometimes attack other pelvic tissues (6). Endometriotic lesions often have an asymmetrical distribution. In the pelvis, more lesions are seen in the posterior chamber and on the left, while lesions in the abdomen and thorax are more on the right site (8). Other mechanisms involved in this disease include unregulated immunity, inflammatory factors, hormones, genetic and epigenetic factors, and environmental causes. They may also have pre-existing endometrial abnormalities which lead to pathological endometrial implantation and growth out of the uterus (9).

Genes play an important role in transmitting the disease from one generation to another. Although the specific gene pattern involved in endometriosis has not been established, many genes can be attributed to endometrial involvement, including genes of cell cycle regulation, inflammation, hormone receptors, growth factors, and adhesion molecules (10). Genetic mutations may interact with other factors, including changes in hormonal hemostasis. They can also be tissue-specific or affect other gene expressions in different tissues (11). Various studies have shown that two chromosomal regions 10q26 and 7p13–15 which have some important genes such as CYP2C19, INHBA, SFRP4, and HOXA10 have a significant role in the transmission of hereditary

endometriosis to the next generation (12). Environmental factors such as endocrine-disrupting chemicals are other influential factors in endometriosis. There is currently no direct evidence of the role of endocrine-disrupting chemicals in endometriosis (13).

Other causes of endometriosis include surgery, hormone therapy, pregnancy, and ovarian stimulation during infertility treatment which may cause by chronic stress, activation of adrenergic pathways, and increased rate of angiogenesis (9). The role of estrogen in endometriosis development has also been well established, the secretion of estradiol by endometriotic lesions in the peritoneal cavity creates a precise endocrine substrate for implantation of many lesions (14). However, another study has shown that the growth of lesions outside the uterus has not continued even in environments with high levels of estrogen. Thus, it can be stated that the presence of estrogen is necessary and not sufficient to cause endometriosis (15). Other cases of endometriosis include its postmenopausal development, which is probably due to the production of extra-ovarian estrogen by endometriotic lesions and adipose tissue (16).

Endometriosis-related Infertility

Several factors are involved in both endometriosis and infertility. Thus, there are different reasons to explain why endometriosis can cause infertility. The type and quality of the relationship between endometriosis and infertility should also be evaluated for effective treatment procedures. In one study, changes in pelvic density, immunological system, and endometrial alterations in baboons with spontaneous endometriosis were found to be associated with infertility. As infertility was also observed in these baboons, possibly it is related to ovulation dysfunction. Research has also shown that fertility rates will decrease more sharply in baboons with moderate to severe endometriosis than in those with mild endometriosis (17).

This disease can adversely affect fertility due to inflammatory changes in the pelvic cavity, ovaries, and uterus, leading to ovarian dysfunction, fertilization changes, uterine endometrial abnormalities, pelvic adhesions, and decreased frequency of sex due to pain (18). In addition, adenomyosis, which is often associated with endometriosis, is also involved in infertility. Adenomyosis is a disease in which the endometrium breaks through the myometrium, causing menstrual cramps, low abdominal pressure, and can lead to heavy blood discharge (19).

Human endometrium decidualization involves a dramatic functional and morphological differentiation of human endometrial stromal cells (ESCs) and is crucial for the formation of an effective pregnancy. Decidualization results from a complex interplay of morphogens, transcription factors, cell cycle regulators, cytokines, and signaling pathways. Progesterone, together with proteins that are regulated by progesterone and/or cyclic adenosine monophosphate procedures a crucial network for decidualization of ESC and is a prerequisite to prosperous implantation. Decidualized ESCs involve in the microenvironment at the feto–maternal interface and its indirect or direct effect on extracellular matrix remodeling, anti-oxidative stress, the local immune response regulation, and angiogenesis. Damage of this procedure is related with some pregnancy disorders, including recurrent miscarriages, infertility, and uteroplacental disorders (20).

Endometriosis-related Pain

There are several mechanisms of pain in endometriosis in which the presence of endometrial cells following retrograde menstruation is considered as the main cause of pain. after implantation of endometriotic lesions in the pelvis, the immune cells (macrophages, mast cells, neutrophils, natural killer cells, dendritic cells, and B and T lymphocytes) in the peritoneal fluid are stimulated to secret large volumes of multiple types of cytokines (TNF-a, IL-10, and TGF-b), chemokines (IL-8), angiogenic growth factors (VEGF), and alarmin (IL-33) (21,14). Endometriotic lesions localized next to nerve fibers lead to continuous stimulation and pain production. Also, peripheral nerves are constantly stimulated and chronic pelvic pain is seen (6). Excessive generation of prostaglandins and inflammatory factors by endometriotic lesions can also lead to myometrium hypertonia and

secondary ischemia resulting in dysmenorrhea (Figure 1B). Thus, it is recommended to treat endometriosis pain as soon as possible to prevent further pathologic events (22).

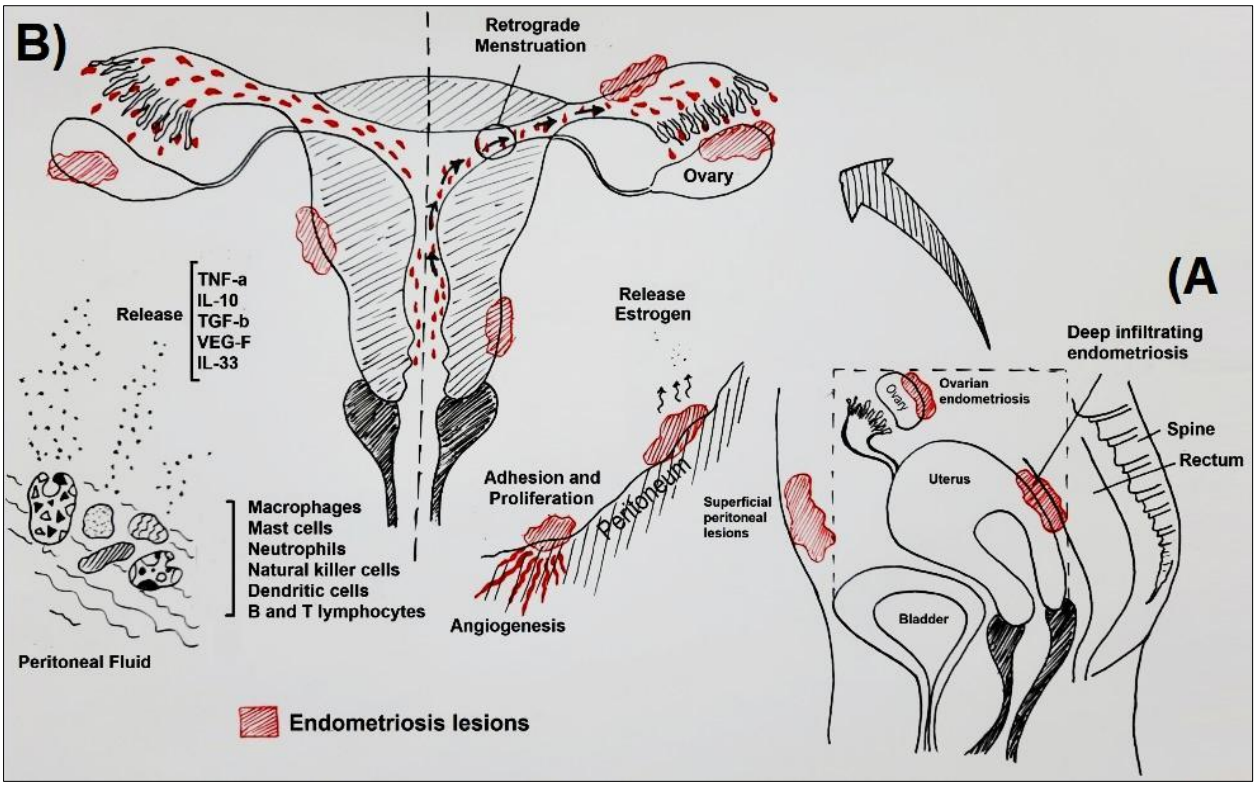

Figure 1. Overview of endometriosis and involved inflammatory factors; A) Superficial peritoneal lesions, ovarian endometrioses, and deep infiltrating endometriosis are three well recognized types of endometriosis due to the origin of lesions. B) Retrograde menstruation is the most important mechanisms involved in endometriosis development which is caused by return of menstrual blood into the fallopian tubes and pelvic cavity. Following implantation and adhesion of endometriosis lesions in the pelvic cavity, immune cells are activated and induce pain by secreting various types of cytokines, chemokines, and immune factors.

Diagnosis

The process of endometriosis diagnosis has always been faced with many difficulties. Symptoms of the disease are general, thus they cannot be definitively attributed to disease. In addition, the pathogenesis of endometriosis is always an ambiguous process. On the other hand, the disease has three different phenotypes in which their simultaneous occurrence makes the diagnosis process more difficult. In some cases, endometriosis co-occurs with adenomyosis complicates the diagnosis and treatment of this disease. But the main problem in diagnosing endometriosis is the presence of pelvic pain as the main symptom which appears in different forms. It is also sometimes associated with other non-gynecological problems, such as gastrointestinal or urinary tract pain, which can lead to confusion of specialists (23, 24). As a result, specialists face a serious challenge in definitively diagnosing endometriosis. Most patients do not show a specific sign during the pelvic and uterine examination, and the diagnosis is usually made by asking questions about the person's clinical history. Regarding the difficulties mentioned in diagnosing pelvic involvement in endometriosis, it is important to state that the patient must be evaluated for other pelvic involvements. Thus, in order to make a definitive diagnosis, ultrasound scans should be performed to ensure the absence of fibroids and ovarian cysts. It is also better to perform pregnancy tests; Pap smears sampling, urine analysis and cell culture, as well as vaginal and cervical sampling (5, 25).

Ultrasonography of pelvic masses is performed in both trans-vaginal and trans-abdominal. Transvaginal ultrasonography provides a better image of pelvic space to detect ovarian endometriosis cysts, but it is not

possible to examine endometriosis adhesions and deep penetrating endometriosis. Some specialists use MRI and CT scans to examine pelvic masses. But in the meantime, the best way to definitively diagnose endometriotic lesions is laparoscopic technique after confirmation of histological specimens (26, 27). However, although laparoscopy is a useful method to disease diagnosing and presenting a complete view of the lesions, it is not the first line of diagnosis due to its invasiveness, need for surgery and the high cost for patients (28, 29). The use of blood biomarkers through blood tests can also be a good alternative to help better diagnose endometriosis because it is less expensive for the patient and relatively non-invasive than laparoscopy. Changes in levels of proteins and microRNAs can be used in this regard (30). Also, research has shown that levels of cytokines, CA-125, and angiogenic and growth factors in women with endometriosis have changed compared to control samples, but they cannot be used as a definitive way to diagnose endometriosis (31, 32). It seems that the diagnosis of endometriosis varies according to the type and location of lesions and it is better to use a combination of all the mentioned methods according to the patient's condition. As a result, more studies are needed in this field to be able to say with certainty the role of techniques in the diagnosis of endometriosis (33).

Management strategies

Due to the difficulty of definitive diagnosis and also the chronicity of endometriosis, the management of this disease also requires more time and continuous follow-up (34, 35). Generally, depending on the patient's condition, the treatment is done in three ways; medication, surgery and ART. The first line of treatment is the use of medicine, which includes hormonal and non-hormonal drugs including analgesics that play an important role in controlling pain caused by endometriosis. The most important analgesic agent is Non-steroidal Anti-inflammatory Drugs (NSAIDs). But hormonal medications include a combination of oral contraceptive (COCs), gonadotropin-releasing hormone analogues (GnRHa) and progestin that help prevent the disease progression. During drug treatment, the disease process decreases and the inflammation and pain caused by endometriotic lesions are reduced. It also costs less for the patient than surgery. On the other hand, the surgery, in addition to being associated with several risks and a recovery period, does not affect retrograde menstruation (36). However, because medical treatments reduce the patient's discomfort, they are not proper for all affected people. Because these drugs prevent ovulation by inhibiting hormonal fluctuations, thus they prevent pregnancy in females. On the other hand, these medications do not cure or eliminate endometriotic lesions, but only reduce the pain and inflammation caused by this pathologic situation (37).

Although surgery has more costs and many side effects, it is the best way to eliminate endometriotic lesions and treat the pain. Studies have shown that removal of endometriotic lesions after surgery represented a significant role in the patient's fertility process and even increases the rate of spontaneous pregnancy (38, 39). Surgery is usually performed in two conservative and definitive ways. The difference between the two methods is excision of the uterus (hysterectomy) and one or both ovaries (oophorectomy) in a second way if needed. Also, in the first method, because the uterus and ovaries are not removed, some lesions may remain due to the extended form of endometriotic lesions spread (6). Sometimes surgery can reduce the function of one or both ovaries, which is especially important in patients with bilateral involvement, advanced gestational age, a history of endometriosis, or infertility. Thus, the decision about surgery should be made with sensitivity and accuracy (5). Surgery procedures to remove endometriotic lesions are performed laparoscopically, except in a few cases where laparotomy is required due to the extensive lesions. However, it should always be considered that lesions are removed during surgery, while the cause of their occurrence is still present, which can explain the reason for the return of endometriotic lesions after surgery (40). Therefore, it is always necessary to apply medications after surgery to prevent the return of lesions (41).

Another way is the application of Assisted Reproductive Technologies (ART) to increase the fertility rate in patients who are infertile after endometriosis because the presence of endometriotic lesions reduces the chance of sperm contact with the ovum in the fallopian tubes. Thus, In Vitro Fertilization (IVF) can help fertility in these patients. However, in order to get better results in these patients, they should be treated with medication

from 3 to 6 months before IVF (41). The strategies for the treatment of endometriosis in different conditions are depicted in Figure 2.

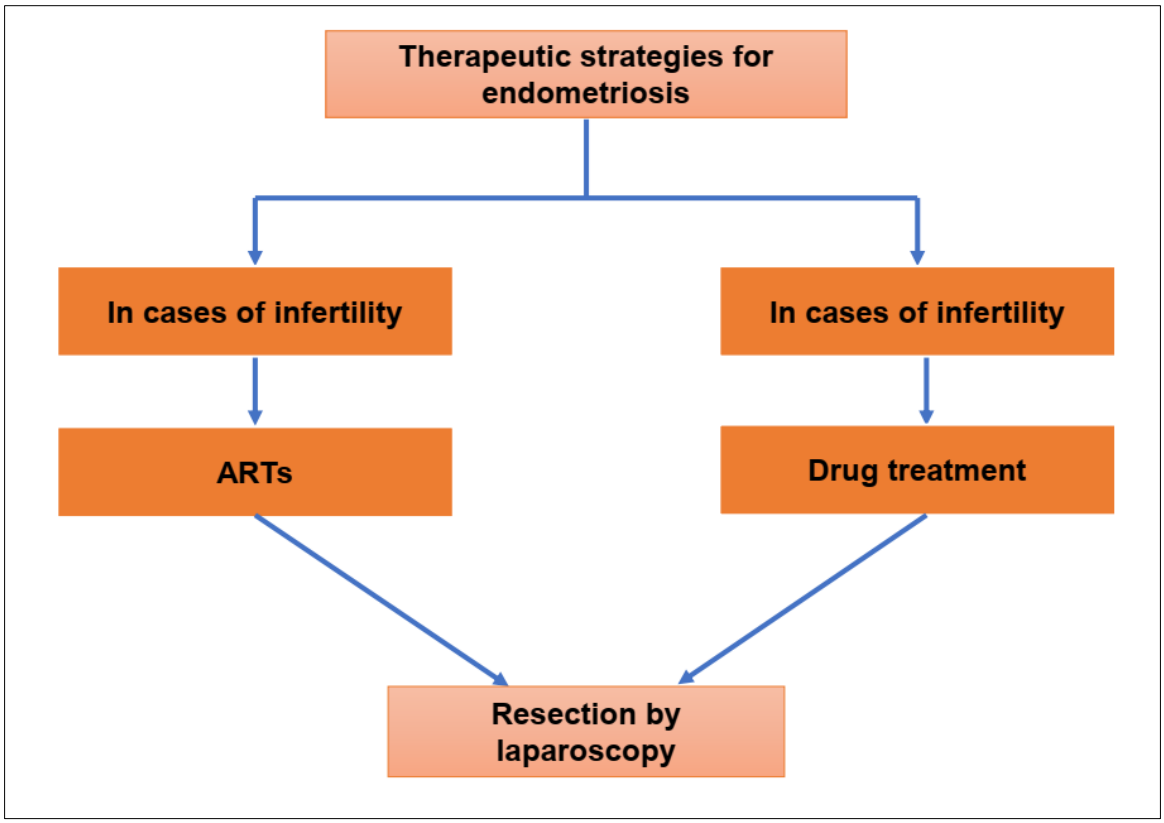

Figure 2. Therapeutic strategies for endometriosis**.** Treatment methods are varied in different conditions. In the case of pain, drug treatments are used, while in cases of infertility, assisted reproductive techniques are used.

Conclusion

Todays, endometriosis, an inflammatory disease associated with chronic pelvic pain, is recognized as a social rather than an individual health problem because it affects 10% of all women around the world. Also, its presence in the reproductive ages disrupts the process of fertilization and even causes infertility. There is still no definitive reason for endometriosis, but numerous findings have suggested the role of genetic, environmental, and inflammatory factors. Currently, the strongest theory for endometriosis is retrograde menstruation, which causes menstrual blood to return to the fallopian tubes and pelvic space, causing endometriotic lesions in these spaces. Depending on the location of lesions, they are divided into superficial peritoneal lesions, ovarian, and deep infiltrating endometriosis categories, Also, depending on the severity of the lesions, four stages are considered. However, in some cases, endometriosis may cause by pelvic surgery, hormonal fertility treatments, menopause, and even pregnancy. Due to the release of many inflammatory factors in the pelvic cavity following endometriosis, patients suffer from chronic pelvic pain.

Also, the lack of fertility in patients who try for this purpose is another important point that shows the need to treat and manage this disease as much as possible. Due to the existence of different phenotypes and the widespread forms of pelvic pain, the process of diagnosing has always been a great challenge for specialists and it can be said that they use a diagnostic package and not just one way. A package that includes non-invasive techniques such as asking about the patient's family history, urine tests, vaginal sampling and ultrasound examinations, and invasive laparoscopic techniques. Of course, laparoscopy provides a much better view for diagnosing the disease, but because it is invasive and expensive, it is usually the last line of diagnosis. Treatment of endometriosis is not definitive and using only one method, so gynecologists use a variety of treatments ranging from the prescription of hormonal medications to reduce pain, inflammation and prevention

of secretion of hormones to surgical removal of lesions. It seems that in all fields such as the definition, diagnosis, and treatment of the disease, there is always disagreement, given the prominent role of the disease in the field of women's health, so a consensus should be reached. Today, with the advancement of technology and extensive studies that have been done in various fields in order to better manage endometriosis, new markers have been identified that can make the diagnosis easier and faster. In this regard, we can mention interferon alpha 2 (IFN-α 2) and tumor necrosis factor (TNF)-alpha inhibitors that have been tested in animal models. It is hoped that in the future endometriosis will be diagnosed and treated more advanced and patients will be less likely to receive aggressive and stressful treatments. Therefore, we need more research on new strategies to help diagnose and treat endometriosis in order to advance women's health.

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