DOMINO, Wiktoria, ŚNIEŻNA, Joanna, FLORCZAK, Wojciech, DZWONNIK, Karol, ZELIK, Urszula, WŁODYKA, Jagienka, TRESTKA, Gabriela, PRZYGODA, Maria, DZIEWIC, Jakub, STĘPIEŃ, Kamila and ADAMCZYK, Sabina. Innovative Diagnostic Approaches and Treatment Strategies for Endometriosis: Current Trends and Future Direction - Review. Quality in Sport. 2025;37:57149. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.37.57149
https://apcz.umk.pl/QS/article/view/57149

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.12.2024. Revised: 17.01.2025. Accepted: 17.01.2025 Published: 20.01.2025.

Title: Innovative Diagnostic Approaches and Treatment Strategies for Endometriosis: Current Trends and Future Direction- Review

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1. Abstract

Endometriosis is a chronic gynecological condition affecting many women of reproductive age, often leading to infertility, pain, and other health issues. Diagnosing this disease is challenging due to its often nonspecific symptoms, and its diagnosis requires advanced imaging techniques and, in some cases, laparoscopy. This paper discusses current diagnostic methods used in endometriosis, such as ultrasonography, magnetic resonance imaging (MRI), and molecular tests. Treatment of endometriosis presents a significant medical challenge due to its chronic nature and the difficulty of managing it. The primary goals of treatment include pain relief, improving the patient's quality of life, preventing disease recurrence, preserving fertility, and reducing the need for surgery. Depending on individual needs, various treatment methods are available, including pharmacological and surgical approaches. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to alleviate symptoms, while hormonal therapies, such as combined oral contraceptives, GnRH agonists, and progestogens, aim to inhibit ovulation and estrogen production to reduce inflammation and slow disease progression. Surgery, typically laparoscopic, is indicated for severe symptoms or advanced

disease. Innovative treatment methods show potential in managing endometriosis, but further studies are needed to confirm their safety and efficacy.

Keywords
Endometriosis, Endometriosis diagnosis, Endometriosis treatment, Alternative therapies for endometriosis

2. Introduction

Endometriosis is a complex condition associated with a chronic, estrogen-dependent inflammatory process. During its course, endometrial tissue, including glands and stroma, develops outside the uterine cavity. These lesions most commonly localize in the pelvic peritoneum, ovaries, or the rectovaginal septum. This leads to a range of symptoms related to pain and abnormal functioning of the reproductive system. The disease affects an estimated 6-10% of women of reproductive age. The peak incidence of endometriosis occurs in individuals aged 25 to 35. In women who suffer from infertility and pelvic pain, this prevalence rises to 30-35%. However, due to a significant number of undiagnosed cases, the actual incidence of endometriosis is likely higher. [1][2][3] Four stages of the disease are distinguished, based on the severity, number, location, depth, and size of the lesions. Stage I represents minimal disease, Stage II mild, Stage III moderate, and Stage IV denotes severe endometriosis. Symptoms of endometriosis, such as dysmenorrhea, dyspareunia, chronic pelvic pain, and fertility issues, often significantly impair the quality of life for affected women. [1] Pelvic endometriosis has three important subtypes, which can impact symptoms and diagnostic approaches. Superficial endometriosis, the most common form, is characterized by lesions on the surface of the peritoneum. Endometrioma is an ovarian cyst filled with dark fluid. Deep endometriosis, extending beyond the peritoneum, can damage pelvic organs such as the intestines, bladder, or ureters. In some cases, different forms of endometriosis may coexist, and its presence requires further investigation, especially if severe pain is present. [4]

3. Symptoms

Symptoms of endometriosis may include: increasing premenstrual pain, pelvic pain, lower back pain, dysmenorrhea, pain during ovulation and intercourse, pain during defecation and urination, irregular menstruation, diarrhea or constipation, blood in stool, infertility, and chronic fatigue. [5]

Additionally, symptoms such as fever, nausea, headaches, depression and anxiety, hypoglycemia, rectal bleeding, and increased susceptibility to infections may also occur. [5]

4. Etiopathogenesis

Many theories explain the development of endometriosis, but none of them are definitive. The most widely accepted theory suggests that endometrial cells reach the peritoneal cavity through retrograde menstruation, where they are typically removed. In endometriosis, this process is disrupted by factors such as cell adhesion, mutations, inflammation, or immunological changes. There are also metaplasia theories, in which normal peritoneal tissue transforms into tissue resembling the endometrium. Endometriosis may also spread through the bloodstream or lymphatic system. [4]

5. Infertility

Infertility is one of the most significant symptoms of endometriosis, greatly impacting the quality of life of affected women. It is estimated that 30–50% of women with this condition are affected, although a causal relationship in cases of mild endometriosis has not yet been definitively confirmed. Infertility is more commonly observed in women with advanced endometriosis, as the disease can distort reproductive organs and hinder the movement of eggs and sperm. However, infertility can also occur in cases of mild endometriosis, which may be linked to an increase in pro-inflammatory factors that impair sperm motility, damage eggs, and even embryos. Endometriosis affecting the ovaries disrupts ovulation and egg production, and additionally, follicular fluid in such patients leads to DNA damage in oocytes through increased production of reactive oxygen species (ROS). The use of antioxidants that neutralize ROS helps to limit this damage, suggesting that oxidative stress may play a key role in infertility associated with endometriosis. [6]

6. Diagnostic methods

Endometriosis, despite its common occurrence, is poorly understood, and its symptoms do not always correlate with the extent of the lesions. However, a retrospective study has shown a relationship between the location of deep infiltrating endometriosis lesions and symptoms. For example, adhesions in the Douglas pouch caused dysmenorrhea, and involvement of the uterosacral ligaments was associated with dyspareunia. [1]

Endometriosis presents a significant diagnostic and therapeutic challenge. The diagnostic process should begin with a thorough medical history and physical examination. A study conducted in the UK on over 5000 women with endometriosis revealed that they were at significantly higher risk of experiencing various symptoms compared to the control group. Women with endometriosis more frequently experienced dysmenorrhea, dyspareunia, abdominal and pelvic pain, heavy menstrual bleeding, and had a history of infertility. [4]

Physical examination should include assessment for tenderness or the presence of nodules in the rectovaginal pouch and sacrouterine ligaments, tenderness of the adnexa, detection of tubo-ovarian masses, thickening of the rectovaginal septum, and the presence of a fixed uterus in retroversion. However, a normal result of such an examination does not rule out the possibility of endometriosis. [3]

The gold standard for diagnosing endometriosis remains laparoscopy, which allows for precise evaluation of the abdominal cavity and histological confirmation of lesions. However, this method is costly and invasive and carries the risk of complications. There is ongoing debate about the appropriateness of this invasive procedure in women with mild pain symptoms and lesions that do not present a significant obstacle. In such cases, patient preferences are taken into account; however, laparoscopy is typically performed only when the expected pain relief outweighs the risks associated with the procedure. Alternatively, transvaginal ultrasonography and magnetic resonance imaging (MRI) are used. Both methods are accurate for detecting large lesions, but they have limited effectiveness for identifying small changes on the peritoneum. Ultrasound and MRI are preferred imaging techniques for detecting ovarian cystic endometriosis. [6] [7] [8]

Biomarkers from blood, endometrial tissue, and urine can assist in diagnosing endometriosis, but they do not allow for precise localization of the lesions. A commonly used biomarker is CA-125, which is often found at elevated levels in patients with endometriosis. However, its levels can also increase in other conditions, which limits its effectiveness as the sole diagnostic tool. [7]

For years, researchers have been searching for genetic tests to identify individuals at risk for endometriosis. An analysis of 17,045 cases revealed 14 genomic regions associated with the risk of this disease. Using SNP technology, 49 copy number variation (CNV) loci were discovered, which were present only in patients with endometriosis. Although these findings point to potential genes, there are still no reliable genetic markers for the precise diagnosis of endometriosis. [3]

An additional diagnostic tool may include patient questionnaires, which facilitate the preliminary diagnosis and identification of individuals at high risk for developing endometriosis. [9]

7. Treatment methods

Treatment of endometriosis presents a significant medical challenge, as it is a chronic and difficult-to-treat condition. In recent years, numerous studies have been conducted to develop new therapies for treating endometriosis. The goal of treatment is to alleviate pain, improve the patient's quality of life, prevent disease recurrence, preserve fertility, and reduce the need for surgery. There are various therapeutic approaches, including pharmacological treatment, surgery, or a combination of both, depending on the individual needs of the patient. Pain in this condition arises from nerve irritation at sites where ectopic endometrial tissue is located, due to inflammatory substances produced during the disease. Inflammation is particularly associated with the cyclical nature of menstruation and the process of retrograde blood flow into the pelvic cavity. Estrogen plays a key role in maintaining the inflammatory state in these tissues. [10]

7.1 NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of chronic inflammatory conditions and to alleviate pain associated with primary dysmenorrhea. They mainly work by reducing symptoms but do not inhibit ovulation. [7] NSAIDs relieve symptoms by blocking the COX enzyme, which is responsible for the production of

inflammatory mediators. While both COX1 and COX2 receptors are present, studies show higher levels of COX2 in ectopic endometrial tissues. Both selective and non-selective COX inhibitors are widely used in pain management. Furthermore, selective COX2 inhibitors, such as rofecoxib, may additionally inhibit the growth of pathological endometrial tissue, indicating their potential therapeutic role. [11] Patients using NSAIDs should be aware of potential side effects, such as stomach ulcers, cardiovascular issues, and the risk of acute renal failure. [7]

7.2 Hormonal Therapy

Effective treatment of pain associated with endometriosis involves inhibiting ovulation and estrogen production. Hormonal therapy aims to induce amenorrhea, creating a low estrogen environment that blocks inflammation and prevents the progression of the disease. [10]

7.2.1 Combined oral contraceptives (COCs)

They are widely used as empirical therapy for pain associated with endometriosis, even without surgical confirmation. [12] Two systematic reviews and a Cochrane review (based on 5 randomized controlled trials) have shown that the use of combined oral contraceptives (COCs) helps reduce pain associated with endometriosis, including dysmenorrhea, pelvic pain, and dyspareunia, and improves quality of life compared to placebo. However, it was noted that these studies had low quality, a high risk of bias, and a short follow-up period. [4] ESHRE guidelines classify them as Grade B in reducing dysmenorrhea, dyspareunia, and non-menstrual pain. The advantages of COCs include good tolerance and low cost, but they contain estrogens, which can lead to progesterone resistance and estrogen dominance. Although oral contraceptives have been widely used in clinical practice for many years due to their effectiveness in alleviating dysmenorrhea, reliable evidence supporting their efficacy in treating endometriosis is lacking. [12]

7.2.2 GnRH Agonists

These drugs initially stimulate the pituitary gland to produce FSH and LH, but their long-term use leads to the suppression of the hypothalamic-pituitary-ovarian axis, resulting in anovulation and hypoestrogenism. This hypoestrogenic state can lead to the regression of endometrial lesions, but prolonged use of GnRH agonists can cause symptoms such as hot flashes, vaginal dryness, reduced libido, sleep disturbances, mood swings, and bone loss. [13] The use of adjunctive therapy, such as low-dose COCs, estrogen or progestogens as

monotherapy, as well as bisphosphonates, tibolone, or raloxifene, can alleviate these side effects without affecting the pain reduction efficacy. [12] Medications such as leuprolide, goserelin, and nafarelin are available as injections or nasal sprays and can provide pain relief for up to 12 months. GnRH agonists are not suitable for women planning pregnancy as they suppress ovulation. [14]

7.2.3 GnRH Antagonists

This group of drugs blocks GnRH signaling, leading to a reduction in estrogen levels without the initial hormone surge seen with GnRH agonists. They act quickly to reduce endometriosis-related pain and have a more favorable side effect profile. They are available in both oral and injectable forms. [3] Elagolix, an oral GnRH antagonist approved for the treatment of endometriosis, works in a dose-dependent manner, suppressing pituitary and ovarian hormones, though ovulation can occur at lower doses. Lower doses reduce side effects such as vasomotor symptoms, vaginal atrophy, and bone density loss. [10] Elagolix has demonstrated efficacy in studies, reducing endometriosis-related pain to a degree comparable to medroxyprogesterone but with a smaller impact on bone density. In phase 3 trials, both lower doses (150 mg daily) and higher doses (200 mg twice daily) effectively reduced dysmenorrhea and pelvic pain over six months, though they caused side effects associated with low estrogen levels. Long-term use (12 months) confirmed sustained pain reduction without new safety concerns. Since elagolix does not suppress ovulation, non-hormonal contraception is necessary. [10]

7.2.4 Progestogens

Progestogens act on progesterone receptors (PR), leading to reduced levels of FSH and LH, inhibition of ovulation, and a hypoestrogenic state. This results in amenorrhea and suppression of endometriosis. They also exhibit anti-estrogenic effects by modifying the endometrial structure, suppressing inflammation, inducing apoptosis of endometriotic cells, reducing oxidative stress, inhibiting angiogenesis, and suppressing the expression of matrix metalloproteinases. All these mechanisms contribute to halting the progression of endometriosis and reducing pain. [15] According to ESHRE guidelines, progestogens are the preferred treatment for endometriosis, as they show similar effectiveness in reducing symptoms and pain compared to GnRH agonists, but are more cost-effective and cause fewer adverse effects. [15] Progestogens can be administered orally, intramuscularly, subcutaneously, or via an intrauterine system (IUS). [15] The progestogens that have been

studied and used for treating endometriosis include cyproterone acetate, dienogest, dydrogesterone, gestrinone, lynestrenol, medroxyprogesterone acetate, megestrol acetate, and norethindrone acetate. [14] The use of the levonorgestrel-releasing intrauterine system (LNG-IUS) reduces pain and improves patient satisfaction; however, it is not effective for ovulatory pain because it does not suppress ovulation. [3]

7.2.5 Danazol

Danazol is a synthetic steroid with a structure similar to testosterone. It inhibits steroidogenesis in the adrenal glands, ovaries, and testes, and binds to sex hormone-binding globulins, thereby increasing the concentration of free sex hormones. It also exhibits apoptosis-inducing and cytotoxic effects. [16] Studies have shown that the use of danazol, both as monotherapy and as an adjunct to surgical treatment, is effective in reducing painful symptoms of endometriosis compared to placebo. Additionally, laparoscopic observations demonstrated improved conditions in patients treated with danazol compared to those in placebo groups or untreated groups. [17] In recent years, its use has significantly declined due to numerous side effects. [14]

7.2.6 Selective Progesterone Receptor Modulators (SPRMs)

SPRMs are a new class of synthetic steroids specifically designed to compete with progesterone for binding at the progesterone receptor in a tissue-specific manner. [18] They act as agonists or antagonists. In the absence of progesterone, SPRMs function as mild progestogens, whereas in the presence of progesterone, they may exhibit weak antiprogestogenic effects, particularly in endometrial tissue. [19] They inhibit ovulation without causing systemic estrogen deprivation effects, as estradiol levels remain within the normal range. SPRMs act on the endometrium by suppressing proliferation, reducing bleeding, and decreasing prostaglandin production. [19] Mifepristone and asoprisnil are the most well-studied SPRMs. Research has shown variable efficacy of mifepristone in managing endometriosis-related pain, while asoprisnil has demonstrated a reduction in dysmenorrhea compared to placebo. Ulipristal acetate has been evaluated for its effect on endometriotic lesions, showing improvement in 58% of cases; however, there is insufficient data to conclusively assess its safety and efficacy. [19] Common side effects of SPRMs include headaches, abdominal pain, and breast tenderness. These drugs cause endometrial changes known as progesterone receptor modulator-associated endometrial changes (PAEC). Estrogen levels remain stable, and bone mineral density is unaffected. Further randomized studies are

needed to better evaluate the potential benefits of SPRMs in treating endometriosis-related pain and to examine their long-term safety and impact on the endometrium. SPRMs appear to be a promising option for the medical treatment of endometriosis. [19]

7.2.7 Aromatase Inhibitors

Aromatase inhibitors are a class of drugs that work by blocking the enzyme cytochrome P450 aromatase, which inhibits estrogen production. [7] Since the late 1990s, studies have shown that aromatase P450 is excessively present in both eutopic and ectopic endometrial tissues in women with endometriosis, which is not observed in healthy women. The expression of this enzyme is higher in epithelial cells than in stromal cells. It has also been noted that endometrial changes may create an environment conducive to excess estrogen. For this reason, aromatase inhibitors have been used in the treatment of pain in premenopausal women with endometriosis, based on earlier findings regarding the role of aromatase P450 in this disease. [20] Clinical studies on aromatase inhibitors have yielded mixed results. Treatment with anastrozole and goserelin following endometriosis surgery prolonged pain-free intervals and reduced the risk of recurrence. In another study, letrozole and triptorelin had no effect on pregnancy rates or symptom recurrence. Letrozole, danazol, or placebo therapy reduced pain, but the placebo effect was short-lived. [19] Open-label studies showed that letrozole combined with norethindrone acetate alleviated pain, but symptoms returned after 3 months. Combining letrozole with combined oral contraceptives (COCs) improved pain outcomes but led to ovarian cysts. Vaginal administration of anastrozole did not improve chronic pelvic pain. Aromatase inhibitor therapy is often associated with side effects such as headaches, hot flashes, muscle aches, mood changes, and breakthrough bleeding. It also significantly lowers estradiol levels and may lead to bone density loss. There is no clear evidence supporting the effectiveness of aromatase inhibitors in the treatment of pain associated with endometriosis. The main limitations of their use include symptom recurrence after the therapy is discontinued, severe side effects, and high treatment costs. [19]

7.2.8 Alternative Pharmacological Treatments

Neuroangiogenesis and angiogenesis are key factors in the progression of endometriosis. Anti-angiogenic agents can inhibit the development of early lesions. Substances with anti-angiogenic properties include growth factor inhibitors, COX-2 inhibitors, endogenous angiogenesis inhibitors, plant-derived compounds, immunomodulators, dopamine agonists,

PPAR receptor agonists, progestogens, and GnRH agonists. The proven effectiveness of these agents underscores their potential to slow the progression of the disease. [21]

Angiogenesis Inhibitors

They prevent the formation of new blood vessels by targeting angiogenic factors and tyrosine kinases. Bevacizumab, an anti-VEGF antibody, effectively suppresses endometrial lesion proliferation, reduces vascular density, and lowers VEGF levels. Ranibizumab diminishes the size of endometrial implants, while thalidomide decreases VEGF-A and MPO levels. Sunitinib reduces endometrial cysts, causing their regression in some rats and simultaneously increasing apoptosis. These agents show potential in treating endometriosis due to their anti-angiogenic and anti-inflammatory properties. [21]

TNFα blockers

TNFα is a pro-inflammatory cytokine found in elevated concentrations in the peritoneal fluid of women with endometriosis, correlating with disease severity. TNFα-blocking agents, such as infliximab and etanercept, have been studied as potential treatments for endometriosis. In animal models, these agents reduced the number and size of lesions and inflammatory cytokine levels. However, evidence in humans remains limited. A study on infliximab showed no significant pain improvement compared to placebo. Further research is needed to assess their therapeutic potential in endometriosis management. [14]

Statins

Statins, primarily known for lowering cholesterol levels, also have anti-inflammatory and antiproliferative properties, suggesting their potential application in the treatment of endometriosis. Studies have shown that lovastatin can stimulate osteogenic and adipogenic differentiation and reduce the expression of stem cell markers. Additionally, it reduces angiogenesis and supports implantation and decidual development. Statins may represent a promising solution for treating endometriosis, offering clinical benefits without affecting estrogen, but further clinical studies are needed to confirm their efficacy and safety. [22]

Dopamine and its agonist

Dopamine and its agonists, such as cabergoline, reduce the activity of endometriotic lesions and cell proliferation in animal models. They work through the dopamine pathway, which

influences angiogenesis processes, limiting the growth of new blood vessels. Cabergoline inhibits the development of endometriosis in rats and is more effective in reducing endometrioma size compared to luteinizing hormone-releasing hormone (LHRH) agonists. Quinagolide, another dopamine agonist, lowers the levels of IL-6 and VEGF in peritoneal fluid, showing potential use in the treatment of endometriosis. These drugs may regulate angiogenesis processes and inflammation related to the immune system. [21]

7.3 Surgical treatment of endometriosis

Surgical treatment of endometriosis involves removing endometrial lesions and releasing adhesions to restore normal pelvic anatomy. In the past, open surgeries were commonly used, but nowadays, the laparoscopic method is predominantly employed. Treatment may include excision of lesions, diathermy, or ablation. [23] Indications for surgery include severe pain symptoms, failure of pharmacological treatment, severe and advanced disease with significant anatomical impairment, infertility related to endometriosis, and endometrial ovarian cysts. [5][24] The primary goal of conservative surgery in the treatment of endometriosis is the removal or destruction of visible lesions, while preserving the uterus and ovaries and restoring natural pelvic anatomy. [24] Surgical removal of lesions does not always lead to lasting improvement in quality of life – it has been reported that abdominal pain recurred in 21.5% of patients after 2 years and in 40-50% after 5 years following laparoscopy. In cases of ovarian cysts related to endometriosis (endometriomas), laparoscopic cystectomy is recommended, as it is more effective than drainage or ablation, which are associated with a higher risk of disease recurrence. [6] The ultimate solution for treating endometriosis is total hysterectomy with bilateral salpingo-oophorectomy and thorough excision of all visible endometrial lesions. This procedure is usually performed in women with advanced disease who have completed their family planning or in those who experience persistent pain despite less radical treatments. [24]

7.4 Interruption of Pelvic Nerve Pathways:

The effectiveness of laparoscopic pelvic nerve interruption in treating dysmenorrhea associated with endometriosis was evaluated in a Cochrane review. The studies indicated that laparoscopic uterosacral nerve ablation did not provide additional benefits after one year. In contrast, presacral neurectomy (PSN) proved more effective in alleviating pain and improving

quality of life at both 6 and 12 months. However, PSN was associated with a higher risk of adverse effects, such as bleeding and constipation. [23]

7.5 Physical Therapy

Physical therapy in the treatment of endometriosis encompasses various aspects, including pre- and postoperative rehabilitation, scar therapy, and pelvic floor rehabilitation. It focuses on kinesiology, manual therapy for the pelvic and lumbar regions, balneotherapy, and visceral manipulation. Physical exercises, self-care, and relaxation techniques are also essential, as they assist patients in managing symptoms and enhancing their quality of life. [25]

7.6 Alternative treatment

Patients with endometriosis often seek alternative methods for symptom relief, such as dietary changes, physical exercise, or acupuncture. Acupuncture has been shown to reduce pelvic pain, as confirmed by a meta-analysis, although treatment protocols varied in terms of frequency and duration. Research on physical activity has yielded mixed results. Dietary modifications, such as avoiding gluten or dairy, may reduce pain perception but do not improve quality of life. Evidence supporting the benefits of nutritional supplementation is also limited. [3]

7.7 Future Treatment Options

A promising approach to treating endometriosis could involve replacing damaged stromal cells of the endometrium with healthy ones. Induced pluripotent stem cells (iPSCs) enable the creation of various cell types, including healthy stromal cells of the endometrium, which could be utilized in therapy. Research has demonstrated that skin fibroblasts from patients can be reprogrammed into iPSCs and subsequently differentiated into healthy, progesterone-responsive endometrial cells under hormonal and molecular control. While this technology holds potential for future regenerative therapies, numerous technical challenges still need to be resolved. [10]

8. Conclusion

Endometriosis remains a significant challenge in both diagnosis and treatment. Currently, there is no ideal diagnostic method that allows for rapid, accurate, and non-invasive detection of the disease. Existing approaches, such as laparoscopy, although effective, are invasive and

carry a risk of complications. Therefore, further research is essential to develop new, more precise, and less burdensome diagnostic tools for patients.

Similarly, there is no universal solution for the treatment of endometriosis. Available methods include pharmacological treatments, such as nonsteroidal anti-inflammatory drugs, hormonal therapies, or innovative pharmaceutical agents, as well as surgical treatments, including laparoscopic excision of lesions. While each of these approaches can effectively alleviate symptoms and improve patients' quality of life, none guarantees a permanent cure and all are associated with a risk of recurrence. This highlights the necessity for ongoing research into new therapies that are not only more effective but also safer and better tailored to the needs of patients, particularly those of reproductive age.

These conclusions underscore the importance of investing in scientific research on endometriosis, which has the potential to lead to significant breakthroughs in the diagnosis and treatment of this condition.

Author's Contribution:

Conceptualization: WD,GT; methodology: WD, JŚ, JD; software: WF, UZ; check: GT, WF and MP; formal analysis: MP, SA, JW; investigation: WD, KS; resources: GT, KD, JW, WF; data curation: WD, KS, WF, JW; writing - rough preparation: JŚ, WF, JD; writing - review and editing: WD, UZ, KD, MP; visualization: JŚ, UZ, GT; supervision: WD, KS,WF; project administration: WD, SA, MP, KD, JD, JW;

All authors have read and agreed with the published version of the manuscript.

Funding Statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors declare no conflict of interest.

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