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Endometriosis – Treatment Methods and the Impact of Physical Activity on Symptoms

Iwona Pudełko University
Clinical Hospital in Wrocław
Borowska 213 Street, 50-556 Wrocław
i.pudelko.97@gmail.com
https://orcid.org/0009-0001-6403-4141

Filip Klimas
SP ZOZ MSWiA Hospital in Kraków
Kronikarza Galla 25 Street, 30-053 Kraków
e1filipklimas@gmail.com
https://orcid.org/0009-0000-5266-8676

Zuzanna Zięba
University Clinical Hospital in Poznan
Przybyszewskiego Street 49, 60-355 Poznań
zuzia1997.z@gmail.com
https://orcid.org/0009-0002-1576-8058

Adriana Potoczek
University Clinical Hospital in Katowice
Medyków 14 Street, 40-752 Katowice
adriana.potoczek@interia.pl
https://orcid.org/0009-0002-3981-3490

Dorota Zatłoka-Mazur
Tytus Chałubiński Regional Hospital in Zakopane
Kamieniec 10 street, 34-500 Zakopane
zdorota811@gmail.com
https://orcid.org/0009-0003-3663-1891

Kacper Rusiński
University Clinical Hospital in Poznan
Przybyszewskiego Street 49, 60-355 Poznań
kacper.rusinski1@gmail.com
https://orcid.org/0009-0005-4002-9267

Kinga Kurenda
SPZOZ District Railway Hospital in Katowice
Panewnicka 65, 40-760 Katowice
kinga.kurenda@wp.pl
https://orcid.org/0009-0000-8908-2556

Adam Jan Ząbek
Katowice Oncology Center
ul. Raciborska 26, 40-074 Katowice, Poland
adamzabek@vp.pl
https://orcid.org/0009-0003-6799-1814

Izabela Lekan
St. John Paul II Mazovian Provincial Hospital in Siedlce, Poland
Księcia Józefa Poniatowskiego 26, 08-110 Siedlce, Poland
izaabelalekan@gmail.com
https://orcid.org/0009-0000-5079-9795

Klaudia Ostrowicz,
Upper Silesian Medical Center of Prof. Leszek Giec SUM
Ziołowa 45/47, 40-635 Katowice
ostrowiczklaudia@gmail.com
https://orcid.org/0009-0008-4098-7213

ABSTRACT

Endometriosis is a leading cause of chronic pelvic pain in women of reproductive age, significantly impacting the quality of life. Numerous hypotheses regarding the etiology of endometriosis and its diverse clinical presentation limit the effectiveness of treatment to symptom management, as there is no targeted cure. This review presents the current understanding of how physical activity may contribute to the management of symptoms associated with endometriosis and summarizes the therapeutic strategies employed.

Keywords: endometriosis, treatment of endometriosis symptoms, medical therapy, pelvic pain, physical activity

Introduction

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissue outside the uterine cavity. Endometrial implants are primarily found in the pelvic cavity but can also be located in the ovaries, fallopian tubes, intestines, and various parts of the abdominal cavity [1]. The development of this hormonally independent disease can lead to infertility and is associated with high treatment costs [2]. Diagnosis presents a challenge, as no symptom is specific to endometriosis, and managing the disease therapeutically is also difficult, focusing on symptom alleviation [9]. Endometriosis is characterized by chronic pelvic pain in women of reproductive age, significantly impairing quality of life, and there is still no targeted cure for it [11]. Current therapeutic strategies focus on long-term symptom relief and preserving fertility [38,39]. Medications are only effective in treating pain associated with endometriosis [2], and the degree of disease progression is not always correlated with the pain symptoms reported by patients [47,37]. There is growing interest in utilizing physical activity as a non-pharmacological approach to modify the pain symptoms of endometriosis [12].

Materials and Methods

This study is based on scientific publications obtained from the PubMed database. The referenced articles primarily address the pathophysiology of endometriosis, its associated symptoms, and treatment methods, including both pharmacological and surgical approaches, as well as the impact of physical activity on the modification of pain-related symptoms.

The Pathophysiology and Epidemiology of Endometriosis

The pathogenesis of endometriosis is complex, and the mechanisms associated with it are not fully understood. A key role is played by the inflammatory pathway, hormonal regulation, and angioneurogenesis. As such, managing the long-term complications associated with endometriosis remains a challenge [4]. The most widely accepted hypothesis is retrograde menstruation, which suggests that fragments of menstrual tissue flowing through the fallopian tubes contribute to the seeding of endometrial cells and their implantation in the peritoneal cavity [8]. Endometriosis is also defined as a "steroid-dependent" disorder, as it depends on cell-specific patterns of steroid receptor expression and hormone metabolism, which vary depending on the menstrual cycle phase [43,44]. It has also been found that the peritoneal fluid in patients with endometriosis contains elevated levels of pro-inflammatory cytokines [48,49,50].

It is observed that 90% of patients with clinically confirmed endometriosis suffer from dysmenorrhea, 76% experience dyspareunia, 77% have chronic pelvic pain, 66% experience dyschezia, and 15% have hematochezia [3]. Chronic inflammation can lead to systemic effects, including metabolic disturbances, cardiovascular diseases and immune dysregulation. The complex etiology of endometriosis and its diverse presentation limit the effectiveness of treatment. There is also a high risk of recurrence and intolerable side effects from medications, which leads to poor adherence to medical recommendations [13]. Some women experience recurrent, especially perimenstrual, changes in bowel movements (diarrhea or constipation), irritable bowel syndrome, and bloody stools, suggesting evidence of deeply infiltrating endometriosis in the lower gastrointestinal tract [47]. Neurological changes and chronic inflammation in endometriosis exacerbate the perception of pain, anxiety, fatigue, and even depression [45,46].

Treatment Methods

Hormonal therapies and surgery are among the main treatment methods used; however, they have limitations and do not address all the aspects of the problems caused by endometriosis. Physical activity and exercise have been suggested in numerous studies as alternative treatment options [2]. Current therapeutic strategies focus on long-term symptom relief and fertility preservation [38,39].

- Progestogens induce anovulation and pseudo-decidualization of the endometrium by acting as natural progesterone. This leads to the atrophy of endometriotic implants by reducing angiogenesis and inflammation [40,41,42].

- Currently, first-line treatment for symptomatic endometriosis and prevention of recurrence after surgery is achieved with tablets containing only progestogens, including dienogest, norethisterone, and medroxyprogesterone [34,35,36].

- Dienogest, a 19-nortestosterone derivative, has the potential to overcome progesterone resistance by increasing PRβ expression in endometriotic lesions [27]. Several randomized controlled trials have demonstrated its effectiveness in treating pain associated with endometriosis across various phenotypes [31,32,33]. Dienogest allows for the reduction in the size of ovarian endometriomas without decreasing ovarian

reserve [28,29,30]. It also alleviates pain symptoms related to deeply infiltrating endometriosis, thereby significantly improving the quality of life for patients [27].

- A GnRH agonist, initially in treatment, may cause a flare effect due to the stimulation of gonadotropin secretion, caused by the replacement of the native L-amino acid with a D-amino acid in the sixth position of the native GnRH peptides. Over time, however, it reduces estrogen production through downregulation and desensitization of pituitary GnRH receptors [26].

- An induced hypoestrogenic state can also lead to the regression of endometriotic lesions. However, prolonged receptor occupancy results in vasomotor symptoms, vaginal dryness, sleep disturbances, decreased libido, mood disorders, and bone mass loss [25].

- Elagolix is an orally administered GnRH antagonist [7], a uracil derivative, and the first approved compound effective in reducing moderate to severe pain associated with endometriosis [23,24]. Its ability to partially suppress estradiol, unlike GnRH agonists, prevents the development of a hypoestrogenic state in patients, thereby reducing side effects. It has been shown to effectively reduce symptoms such as lower abdominal pain and dysmenorrhea, contributing to improved work productivity and overall quality of life. However, the use of Elagolix is not recommended for patients who have not responded to treatment with GnRH agonists or antagonists, as well as for pregnant women and patients with osteoporosis or severe liver failure [7].

- Aromatase inhibitors (e.g., Anastrozole, Letrozole) are selective progesterone receptor modulators (SPRM, e.g., Mifepristone, Anoprisnil) or selective estrogen receptor modulators (SERM, e.g., Bezedoxifen, Raloxifene). However, aromatase inhibitors are associated with a high rate of adverse effects, which is why the guidelines from the European Society of Human Reproduction and Embryology (ESHRE) recommend their use only in research settings or in combination with other medications for women who are resistant to other traditional hormonal therapies [14].

- Direct analgesia using nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or various opioids is often used as first-line treatment alongside hormonal therapy.

NSAIDs are widely used in the treatment of chronic inflammation and are effective in alleviating pain symptoms. They inhibit the production of prostaglandins and inflammation by blocking cyclooxygenase enzymes [15].

Natural Products and Dietary Supplements

Natural products and dietary supplements can serve as an adjunct to the primary treatment of endometriosis. Substances such as curcumin (found in the roots of *Curcuma longa*), green tea (flavonoids), omega-3 polyunsaturated fatty acids, and resveratrol (found in fruits such as berries) possess antioxidant, anti-inflammatory, anti-angiogenic, and anti-mitotic properties [19,20,21,22].

The natural products mentioned above contain bioactive compounds that reduce the expression of pro-inflammatory cytokines such as IL-6, IL-8, TNF-α, and COX-2, thereby decreasing the expression of VEGF and the activity of matrix metalloproteinase-9. This ultimately inhibits the progression of endometriosis [17,18].

Surgery

Not every medical therapy will be effective or suitable for all subtypes of endometriosis. For patients who are resistant to pain management treatments and intolerant of the side effects of medical therapies, surgical excision of all visible endometriotic lesions is considered an alternative treatment [15,16]. In women who wish to conceive while preserving natural fertility and enhancing assisted conception, fertility-preserving surgery, known as conservative surgery, is preferred. This approach focuses on resecting endometriotic lesions while preserving the ovaries and uterus [14].

Treatment Selection for Endometriosis

The severity of symptoms, the extent and location of the disease, as well as the patient's desire for children and age, are the main factors that determine the choice of treatment for endometriosis. Treatment methods are based on pharmacology, surgery, complementary use of natural products, and appropriate physical activity. Often, a combination of various methods is used in treatment. Pharmacological therapy for endometriosis aims to alleviate symptoms or prevent postoperative disease recurrence [5]. Treatment methods such as hormones and surgery have limitations and do not address all dimensions of the issues caused by endometriosis. Physical activity and properly selected exercises are often suggested as an alternative for symptomatic treatment and as a complement to other treatment methods [2].

Oral contraceptive pills, danazol, gestrinone, medroxyprogesterone acetate, and gonadotropin-releasing hormone agonists (GnRH-a) form the basis of hormonal treatment for endometriosis.

A new class of drugs known as aromatase inhibitors also represents a potential therapeutic option for endometriosis, although their use is associated with numerous side effects [6].
Hormonal modification remains the cornerstone of endometriosis treatment in both the initial diagnosis and long-term maintenance therapy. The current strategy for managing endometriosis focuses on alleviating associated symptoms, avoiding recurrent surgeries, and, in young women planning pregnancy, prioritizing fertility preservation and potential reduction of systemic effects that may persist throughout life. [4].

The Impact of Physical Activity on Symptom Severity

Recent studies suggest that physical activity has a beneficial impact on pain perception and quality of life in women, provided it is appropriately tailored to the individual physical capabilities of patients, while also avoiding high-intensity sports during painful menstruation. Regular physical activity should contribute to both physical and mental well-being in women with endometriosis, in combination with appropriately selected pharmacological or surgical treatments. Physical activity that combines endurance, stretching, and flexibility at light or moderate intensity has been shown to be particularly beneficial. [9] Numerous studies suggest positive outcomes for patients with endometriosis who engage in exercise either exclusively or in combination with other therapies. Improvements have been noted in pain levels, quality of life, anxiety, and even depression. [11].
In one study, pelvic pain was assessed using a visual analog scale through questionnaires. The data were statistically analyzed. A total of 81 patients complaining of persistent pelvic pain with intraoperative and histologically confirmed endometriosis were examined. Thirty-one of them (38.2%) regularly engaged in sports as part of their daily life routine, while 50 (61.8%) did not engage in any physical activity. Among those without physical activity in their daily life, 33 patients reported effective pain relief from pelvic pain, while only 14 patients in the regular exercise group reported similar effectiveness. The effectiveness of pain relief was achieved in 66% of women not engaging in any physical activity and 45.1% of women who regularly exercised (statistically significant difference, $p<0.05$). Based on the results, it can be concluded that the effectiveness of pain relief medications may be lower in patients with endometriosis who engage in regular daily physical activity. [10].
There is a growing interest in using exercise as an alternative, non-pharmacological pain relief method in the treatment of endometriosis to improve the comfort and quality of life of patients. One study aimed to assess the impact on pelvic pain caused by endometriosis following a single session of "supervised" exercises delivered via telemedicine compared to "self-

managed" exercises in virtual reality (VR). The study suggested that a single session of "self-managed" exercises delivered through VR could be as effective as a single session of "supervised" exercises provided via telemedicine, which, according to the study authors, provides immediate relief from pelvic pain associated with endometriosis [12].

Discussion

Current strategies for treating endometriosis are not targeted; they primarily focus on alleviating associated symptoms, avoiding repeated surgeries, preserving fertility, and reducing the systemic effects that may affect women with endometriosis throughout their lives. Hormonal modification remains the cornerstone of endometriosis treatment, from initial diagnosis to long-term maintenance therapy. Women with endometriosis symptoms who wish to conceive face limited therapeutic options [4]. Despite several treatment methods available, there is still no targeted cure for this disease [11]. The pharmacological therapy for endometriosis aims to reduce pain and other discomforting symptoms associated with the condition [5]. Current research results show promising potential benefits from incorporating appropriate physical activity into the treatment of patients with endometriosis, as well as the synergy between exercise and hormonal therapies in managing symptoms related to the disease. However, the current lack of high-quality, robust studies investigating these aspects of endometriosis treatment is a significant barrier to progress in this field [11].

Conclusion

Hormonal regulation, angiogenesis, and the inflammatory pathway play a crucial role in the complex pathogenesis of endometriosis. The mechanisms associated with endometriosis are not fully understood, and managing the long-term complications related to the disease remains a challenge. For clinicians to incorporate exercise into the treatment of endometriosis, clear guidelines and recommendations regarding its benefits are needed. Furthermore, current clinical guidelines for endometriosis do not reflect the mentioned benefits of exercise. The scientific literature indicates that physical exercise is a beneficial factor in treating symptoms related to endometriosis. Exercise offers the potential to provide women with a non-invasive, non-pharmacological method of symptom control. Research suggests positive effects for patients with endometriosis who engaged in exercise, either alone or in combination with other therapies. There is still no targeted cure for this disease, and hormonal modification remains the foundation of treatment, both in the initial diagnosis and in long-term maintenance therapy.

Authors' contribution: Iwona Pudełko, Filip Klimas, Dorota Zatłoka-Mazur, Zuzanna Zięba, Adrianna Potoczek, Kacper Rusiński, Adam Jan Ząbek, Izabela Lekan, Klaudia Ostrowicz, Kinga Kurenda.

Conceptualization: Iwona Pudełko, Kacper Rusiński, Filip Klimas.

Methodology: Iwona Pudełko, Zuzanna Zięba, Dorota Zatłoka-Mazur, Adrianna Potoczek, Adam Jan Ząbek.

Investigation: Iwona Pudełko, Filip Klimas, Adam Jan Ząbek, Dorota Zatłoka-Mazur, Zuzanna Zięba, Adrianna Potoczek, Kacper Rusiński.

Sources: Zuzanna Zięba, Adrianna Potoczek, Dorota Zatłoka-Mazur, Kacper Rusiński, Filip Klimas.

Formal Analysis: Iwona Pudełko, Izabela Lekan, Klaudia Ostrowicz.

Supervision: Iwona Pudełko, Kinga Kurenda, Kacper Rusiński.

Validation: Iwona Pudełko, Filip Klimas, Adrianna Potoczek, Dorota Zatłoka-Mazur, Zuzanna Zięba.

Writing- Orginal Draft: Iwona Pudełko, Filip Klimas, Dorota Zatłoka-Mazur, Zuzanna Zięba, Adrianna Potoczek, Kacper Rusiński, Adam Jan Ząbek, Izabela Lekan, Klaudia Ostrowicz, Kinga Kurenda.

Writing –Review & Editing: Iwona Pudełko, Zuzanna Zięba.

Project administration: Iwona Pudełko, Filip Klimas, Kacper Rusiński.

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