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Endometriosis in Focus: Modern Therapeutic Approaches for Enhanced Patient Outcomes - Review

Authors

Magda Piekarska, orcid.org/0000-0002-3583-8802 Bielanski Hospital, Cegłowska 80, 01-809, Warsaw madzia12792@gmail.com

Anna Wojtkiewicz, District Medical Centre in Grójec, 10 Piotra Skargi Street 05-600 Grójec, Poland; https://orcid.org/0009-0002-3451-124X anna.a.wojtkiewicz@gmail.com

Zuzanna Kudas, https://orcid.org/0009-0009-6750-6886 Independent Public Complex of Health Care Facilities, Marshal Józef Piłsudski in Płońsk, Henryka Sienkiewicz 7, 09-100 Płońsk md.zuzannakudas@gmail.com

Krzysztof Szerej, District Hospital in Sochaczew, Batalionów Chłopskich 3/7, Sochaczew, Poland https://orcid.org/0009-0003-7581-4965 krzychszerej@gmail.com

Mateusz Górka, Voivodeship Integrated Hospital of Stanisław Rybicki in Skierniewice 1 Rybickiego Street 96-100 Skierniewice, Poland https://orcid.org/0009-0004-6201-4691 mateusz.a.gorka@gmail.com

Weronika Stec, https://orcid.org/0009-0009-8495-3573 Independent Public Complex of Health Care Facilities, Marshal Józef Piłsudski in Płońsk, Henryka Sienkiewicz 7, 09-100 Płońsk weronikastec1234@gmail.com

Affiliations

District Medical Centre in Grójec, 10 Piotra Skargi Street 05-600 Grójec, Poland

Independent Public Complex of Health Care Facilities, Marshal Józef Piłsudski in Płońsk, Henryka Sienkiewicz 7, 09-100 Płońsk

District Hospital in Sochaczew, Batalionów Chłopskich 3/7, Sochaczew, Poland

Voivodeship Integrated Hospital of Stanisław Rybicki in Skierniewice 1 Rybickiego Street 96-100 Skierniewice, Poland

Independent Public Complex of Health Care Facilities, Marshal Józef Piłsudski in Płońsk, Henryka Sienkiewicz 7, 09-100 Płońsk

Bielanski Hospital, Cegłowska 80, 01-809, Warsaw

Abstract

Endometriosis (EM) is a chronic condition affecting millions of women globally, characterized by the growth of endometrial-like tissue outside the uterus. This review highlights the latest advancements in understanding and treating endometriosis, focusing on new therapeutic strategies aimed at improving patient care.

The article briefly discusses the pathogenesis of endometriosis and reviews traditional treatment methods, including hormonal therapies (progestins, GnRH agonists, and oral contraceptives) and surgical interventions. It then explores the limitations of these conventional therapies and delves into newer strategies targeting specific molecular pathways, offering more effective symptom relief with fewer side effects.

Emerging treatments that modulate the immune response and reduce inflammation are also examined, along with innovative approaches to pain management, both pharmacological and non-pharmacological. The review further considers alternative and supportive therapies, such as dietary changes, gut microbiota interventions, and complementary treatments like acupuncture, which may improve the overall management of endometriosis.

This review emphasizes the shift toward more personalized, holistic care in treating endometriosis, with a focus on emerging therapies like Aromatase Inhibitors, GnRH receptor antagonists, and hormone receptor modulators. These approaches represent a significant advancement in improving the quality of life for women with this condition.

Keywords: endometriosis, endometriosis treatment, hormonal therapy, gnrh agonists, gnrh antagonists, pain relief, chronic pelvis pain, dietary management, aromatase inhibitors, alternative therapies for endometriosis

1. Introduction

Endometriosis (EM) is a chronic inflammatory disorder characterized by the growth of functional endometrial-like tissue outside the uterine cavity (1,2), which significantly impacts productivity and quality of life in women. EM affects approximately 10-15% of women in their reproductive years, but pinpointing its exact prevalence is difficult due to the diagnostic challenges and the diverse range of symptoms associated with the condition (1).

EM commonly manifests with symptoms such as dysmenorrhea, which occurs in 90% of cases, chronic pelvic pain in 77%, dyspareunia in 76%, and gastrointestinal symptoms like dyschezia in 66% and hematochezia. These symptoms significantly impair physical, sexual, psychological, and social well-being, making EM a critical public health issue (3).

Endometriosis places a substantial burden on those affected, not only by significantly diminishing quality of life but also by posing considerable diagnostic and therapeutic challenges. Studies indicate that diagnosing endometriosis often involves lengthy delays, with an average of 8 years in the UK and up to 12 years in countries like the US (4–6). These delays are primarily due to the wide range of symptoms and the requirement for invasive diagnostic procedures, such as laparoscopy (7). As a result, the disease can progress and become more chronic, complicating its treatment. Although both surgical and medical treatments are commonly employed, surgical intervention, despite its effectiveness in alleviating pain, carries a 40-50% chance of recurrence within five years and can lead to complications, including a diminished ovarian reserve (8,9).

This article aims to provide a comprehensive review of the latest developments in the treatment of endometriosis. By analyzing recent research and comparing current treatment approaches, this review seeks to highlight new strategies that could improve patient outcomes and reduce the burden of this condition.

2. Pathogenesis of Endometriosis

The pathogenesis of endometriosis is a complex process influenced by a variety of genetic, hormonal, and immunological factors. Despite being classified as a benign condition, endometriosis exhibits characteristics similar to malignant diseases, including the ability to disseminate, invade, and undergo hyperplasia (10). Endometriosis is widely acknowledged as a hormone-dependent disorder, with increased estrogen (E2) levels and resistance to progesterone being key aspects of its pathology. However, the precise ways in which these hormonal changes contribute to the onset and progression of the disease remain elusive. Interestingly, cases of symptomatic endometriosis have been observed in postmenopausal women who do not have elevated estrogen levels, suggesting that other mechanisms may also play a significant role (11).

The most widely accepted explanation for the origin of endometriosis is the retrograde menstruation theory, originally proposed by Sampson. According to this theory, during menstruation, endometrial tissue flows backward through the fallopian tubes into the peritoneal cavity, where it can implant and grow. However, the development of endometriosis is likely driven by additional factors, including hormonal imbalances, immune system dysfunction, invasive behaviors, and angiogenesis (12). Additionally, the lymphatic and vascular dissemination theories suggest that endometrial cells may spread through the lymphatic system or bloodstream, potentially leading to the formation of endometriotic lesions in distant parts of the body (13).

Moreover, the stem cell origin theory proposes that undifferentiated peritoneal tissue, ovarian surface epithelium, and mesenchymal stem cells from the endometrium can differentiate into endometrial-like tissue when exposed to retrograde menstrual blood and chronic inflammatory factors (14). This theory emphasizes the significant roles of the immune system and chronic inflammation in the development of endometriosis, illustrating the complexity of the disease and the ongoing need for research to unravel its underlying mechanisms.

3. Traditional Treatments for Endometriosis

3.1. Pharmacological Treatment

3.1.1. Hormonal Therapies:

Progestins:

Progestogens are a key element in the treatment of endometriosis because of their ability to neutralize the effects of estrogen, which is crucial in the disease's development and progression (8). These hormones work by altering estrogen receptors, thereby reducing the proliferation of endometrial tissue. In addition to this, progestins help manage symptoms by decreasing the inflammatory response within endometriotic lesions, which they achieve by lowering cytokine production and reducing the infiltration of immune cells (15). For instance, Dienogest, a fourth-generation progestin, is commonly used due to its strong anti-inflammatory and antiproliferative effects. It inhibits ovulation, decreases estrogen levels, and directly counteracts the impact of estrogen on endometrial tissue, thus limiting the growth and activity of endometriotic lesions. Dienogest is particularly effective in alleviating pain associated with endometriosis, such as dysmenorrhea, dyspareunia, and chronic pelvic pain, and it is favored for its relatively mild hypoestrogenic side effects compared to GnRH agonists (16). Another progestin, Medroxyprogesterone acetate (MPA), is available in both oral and injectable forms and works by suppressing gonadotropin release, leading to a reduced estrogen environment that inhibits the growth of endometriotic tissue. Although MPA is effective in reducing pain, it can lead to side effects like weight gain, mood swings, and decreased bone density, especially with long-term use (17).

GnRH Agonists:

GnRH agonists represent a crucial category of hormonal treatments for endometriosis. These medications initially trigger a temporary increase in gonadotropin release, commonly referred to as the "flare effect". This is followed by a decrease in GnRH receptor activity in the pituitary gland, leading to a marked reduction in estrogen levels. The resulting hypoestrogenic condition simulates menopause, thereby inhibiting the growth and activity of endometriotic tissue. While GnRH agonists are quite effective in alleviating endometriosis-related pain, they are generally reserved as a second-line treatment due to notable side effects such as hot flashes, vaginal dryness, and loss of bone density. To lessen these adverse effects, add-back therapy with low doses of estrogen or progestins is often recommended, enabling more extended use without the severe consequences of long-term estrogen deficiency. Typically, GnRH agonists

are prescribed for short durations, usually between 6 and 12 months, and are considered when other hormonal treatments have proven ineffective or are not suitable (16).

Combined Oral Contraceptives (COCs):

Combined oral contraceptives (COCs) are frequently used as a first-choice treatment for managing endometriosis-related pain. These contraceptives work by preventing ovulation and stabilizing hormonal levels, which results in reduced menstrual bleeding and decreased estrogen stimulation of endometrial tissue. This mechanism helps relieve pain and slows disease progression. COCs are particularly effective in treating symptoms like dysmenorrhea and chronic pelvic pain. The continuous or extended use of COCs, where the hormone-free interval is minimized or eliminated, has been shown to significantly reduce the recurrence of pain. Side effects of COCs may include nausea, breast tenderness, weight gain, and a heightened risk of thromboembolism. Although these risks are generally low, they must be carefully considered, especially in patients with additional cardiovascular risk factors (8).

3.1.2. Non-Hormonal Therapies:

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs): Medications like ibuprofen are often employed to alleviate pain in endometriosis by blocking the cyclooxygenase (COX) enzymes, which play a key role in the production of prostaglandins—molecules that drive inflammation and pain. While NSAIDs are useful for pain relief, their efficacy in treating endometriosis specifically requires further validation. Moreover, the prolonged use of NSAIDs can result in gastrointestinal issues, such as ulcers and bleeding, as well as cardiovascular risks, limiting their suitability for the long-term management of endometriosis symptoms (18).

3.2. Surgical Treatment:

Laparoscopic Surgery: Preference for Laparoscopy: Laparoscopy is generally the preferred surgical method for treating endometriosis due to its less invasive nature. This approach provides better visualization of pelvic structures, enabling more accurate removal of endometriotic lesions (8). Compared to open surgery (laparotomy), laparoscopy is linked with reduced postoperative pain, shorter hospital stays, faster recovery times, and improved cosmetic results. However, in cases of extensive endometriosis involving significant areas of the pelvis or abdomen, a laparotomy may be necessary to ensure thorough lesion removal (19). Robotic-

assisted laparoscopy is an alternative in complex cases, but it is not widely recommended, as it tends to have longer operative times compared to conventional laparoscopy (8).

Surgical Goals: The main objective of surgical treatment for endometriosis is to completely remove endometriotic lesions while preserving the functionality of essential structures and organs, such as the ovaries, bladder, and intestines. However, surgery carries inherent risks. Conservative surgical approaches, like laparoscopic removal of endometriotic deposits, may impair ovarian reserve, potentially damage other organs, and are associated with a significant recurrence rate (8). Research shows that about 19% of patients with endometriomas experience a recurrence of symptoms within five years after laparoscopy. Furthermore, up to 10% of women may need additional surgery within a year of their initial procedure, underscoring the limitations of surgical treatment and the necessity for effective postoperative strategies to prevent recurrence (20).

Hysterectomy: Hysterectomy, which involves the removal of the uterus and sometimes the ovaries (in the case of a total hysterectomy with bilateral salpingo-oophorectomy), is generally considered a last resort for women with severe endometriosis, especially when other treatments have failed. Although this procedure can offer lasting relief from endometriosis symptoms and reduce the likelihood of recurrence, it has significant consequences, such as permanent infertility and potential hormonal changes that may require ongoing management (8).

4.**Aromatase Inhibitors (AIs):**

Aromatase inhibitors (AIs) have gained increasing recognition as an important treatment option for endometriosis, especially for patients who do not adequately respond to conventional hormonal therapies. The rationale for using AIs in endometriosis is since aromatase activity, which is typically absent in normal endometrial tissue, is significantly elevated in ectopic endometrial lesions associated with the disease (21). This heightened aromatase activity leads to increased local estrogen production within these lesions, which worsens the condition by promoting the growth and survival of ectopic endometrial cells.

Letrozole, a triazole-based AI, is one of the most widely studied in the context of endometriosis. It effectively reduces both systemic and local estrogen levels, resulting in the shrinkage of endometriotic lesions and relief from symptoms such as pelvic pain and dysmenorrhea. Additionally, Letrozole has shown promise in improving fertility outcomes for

women with endometriosis by stimulating ovulation and reducing the size of endometriomas. Research also suggests that combining Letrozole with other treatments, like surgery and ovulation induction therapy, can further enhance fertility in women with mild endometriosis (16). However, the estrogen reduction caused by AIs can lead to hypoestrogenic side effects, such as bone density loss, hot flashes, and joint pain (22). To mitigate these side effects, AIs are often used alongside other hormonal therapies, such as progestins, oral contraceptives, or GnRH agonists, to maintain hormonal balance and minimize adverse effects (23).

The use of AIs in treating endometriosis is supported by their ability to not only alleviate pain but also address other symptoms like intestinal and urinary issues, and they have been shown to reduce the size of visible endometriotic lesions, including rectovaginal infiltrating endometriosis and endometriomas (23). Despite these advantages, guidelines like those from NICE and the German society (S2k) do not currently recommend AIs as a first-line treatment for endometriosis. Instead, AIs are considered a second-line therapy, particularly for pain relief in cases where other treatments have been unsuccessful, though the evidence supporting this use is still deemed insufficient (8).

Additionally, AIs have shown potential in treating postmenopausal women with endometriosis, who make up about 2-5% of endometriosis patients. In these cases, where most estrogen production occurs outside the ovaries, AIs have emerged as a viable treatment option (24).

Current research continues to focus on optimizing the use of AIs in endometriosis treatment, investigating the best therapeutic combinations, and identifying specific patient groups that are most likely to benefit from this approach. Generally, AIs are considered a second- or third-line treatment, particularly for severe or persistent endometriosis cases where other hormonal therapies have not been effective.

GnRH Receptors Antagonists

GnRH receptor antagonists represent a promising new category of drugs for treating endometriosis, offering several benefits compared to the traditional GnRH agonists. These antagonists, such as Elagolix, function by directly blocking the GnRH receptors in the pituitary gland, leading to a swift reduction in the secretion of LH and FSH. This suppression effectively halts the stimulation of ovarian estrogen production, creating a hypoestrogenic state that is essential for managing endometriosis (16).

In contrast to GnRH agonists, which initially cause a surge in gonadotropin release before eventually downregulating the GnRH receptors, GnRH antagonists bypass this "flare effect," providing more immediate symptom relief. Elagolix has gained FDA approval for treating moderate to severe pain associated with endometriosis, based on clinical trials showing its effectiveness over a six-month period. Patients who took Elagolix reported significant decreases in symptoms such as dysmenorrhea, non-menstrual pelvic pain, and dyspareunia. However, as with GnRH agonists, the reduction in estrogen levels can lead to side effects, including decreased bone mineral density and menopausal-like symptoms, such as hot flashes and vaginal dryness (25).

Due to the dose-dependent nature of these side effects (26), Elagolix allows for flexible dosing, enabling partial estrogen suppression in patients at higher risk for severe hypoestrogenic reactions. This flexibility makes Elagolix an important option for patients who need a more customized treatment plan. Furthermore, ongoing research is focusing on the long-term safety of GnRH antagonists, particularly concerning their effects on bone health and fertility, which are crucial considerations for women with endometriosis.

Beyond Elagolix, other GnRH antagonists, including SKI2496 and BAY1214784, are currently being studied (16). These non-peptide antagonists have demonstrated strong inhibition of GnRH-mediated signaling in preclinical trials, showing promising pharmacokinetic properties and significant effectiveness in alleviating endometriosis-related symptoms. The development of these drugs underscores the continuous efforts to offer more effective and less invasive treatment options for endometriosis.

Selective Progesterone Receptor Modulators (SPRMs)

SPRMs represent a newer category of medications that have shown potential in managing endometriosis by influencing progesterone receptor activity. These modulators can act as both agonists and antagonists on progesterone receptors, depending on the tissue they target, allowing them to be used flexibly in treatment (16).

Vilaprisan is one of the most extensively researched SPRMs in the context of endometriosis. It initially showed promise in clinical trials by reducing the proliferation and inflammation in endometrial tissues, offering symptom relief. However, during long-term animal studies, safety concerns emerged, leading to the discontinuation of its development (16). Despite this, SPRMs remain a promising area of exploration, with ongoing research focused on

creating safer and more effective modulators to alleviate endometriosis symptoms while minimizing risks.

Selective Estrogen Receptor Modulators (SERMs)

SERMs represent another category of drugs that may be beneficial in treating endometriosis. These agents can act as both estrogen agonists and antagonists, depending on the tissue involved. In the endometrium, for instance, SERMs can function as estrogen antagonists, thereby inhibiting the growth of endometriotic tissue, while preserving the positive effects of estrogen in other tissues, such as bones (16). However, it is noteworthy that Tamoxifen, the first-generation SERM, has been linked to the development of endometriosis in postmenopausal women being treated for breast cancer, along with an increased risk of endometrial hyperplasia, polyps, and cancer with prolonged use (27).

Bazedoxifene (BZA), originally designed to treat osteoporosis, has also been explored for its potential role in managing endometriosis. BZA counteracts estrogen-induced endometrial proliferation without compromising estrogen's beneficial effects on bone and the central nervous system. Preclinical research suggests that Bazedoxifene may reduce the size of endometriotic lesions, inhibit estrogen-driven cell growth, and limit the recruitment of stem cells within these lesions. However, further studies are needed to fully evaluate its effectiveness in managing endometriosis-related pain and to establish its optimal clinical use (16). Additionally, SR-16234, another SERM with strong antagonistic activity towards ER-α and partial agonistic effects on ER-β, is currently under investigation, although its clinical applicability remains to be fully explored (28).

Dopamine Receptor Antagonists

Dopamine receptor antagonists are emerging as a potential approach for treating endometriosis, particularly due to their ability to inhibit angiogenesis and reduce the size of endometriotic lesions. Quinagolide is one such medication that has demonstrated potential in experimental models by limiting the formation of new blood vessels and shrinking lesion size. The drug works by blocking dopamine receptors, which in turn lowers prolactin levels—a hormone that can promote both angiogenesis and lesion growth in endometriosis (29).

Ongoing clinical trials are assessing the effectiveness of Quinagolide, with a particular focus on vaginal administration to maximize its local impact while minimizing broader

systemic side effects (30). This approach could provide a new non-hormonal treatment option for endometriosis, especially for patients who are unable or unwilling to use conventional hormonal therapies.

Interleukins and Cytokine Inhibitors

Interleukins (ILs) are a group of cytokines crucial to the immune system, particularly in driving the inflammatory processes linked to endometriosis. Elevated levels of specific interleukins, like IL-8, are associated with the recruitment of immune cells to endometriotic lesions, where they exacerbate inflammation, pain, and lesion persistence. As a result, targeting these interleukins has emerged as a promising strategy to alleviate the inflammation associated with endometriosis.

IL-8 Inhibitors: A significant advancement in this field is AMY109, a novel antibody that targets IL-8. Preclinical research has demonstrated that AMY109 can effectively reduce inflammation in endometriotic lesions by preventing IL-8 from binding to its receptors on immune cells. This action hinders the recruitment and activation of neutrophils and other inflammatory cells, thereby diminishing the inflammatory environment that supports endometriosis. Currently, a Phase 2 clinical trial is underway to assess the efficacy and safety of AMY109 in human patients, with the primary goals of reducing pain and shrinking lesion size (31).

IL-33 and IL-6 Inhibitors: Other interleukins, such as IL-33 and IL-6, are also being targeted in experimental endometriosis treatments. IL-33 is known for its role in promoting macrophage polarization towards a type that facilitates tissue remodeling and fibrosis, both critical in endometriosis progression. Inhibiting IL-33 has shown promise in preclinical studies by reducing lesion size and proliferation (32). Similarly, IL-6 plays a key role in maintaining the chronic inflammation seen in endometriosis by preventing the apoptosis of ectopic implants. Research involving anti-IL-6 receptor monoclonal antibodies, such as Tocilizumab, has shown reduced lesion size and decreased inflammation levels in animal models, indicating that these inhibitors could offer new therapeutic options for managing endometriosis (33).

Emerging Approaches to Pain Management in Endometriosis:

Recent progress in endometriosis treatment has concentrated on targeting specific biochemical pathways that contribute to pain and inflammation. One key area of development involves inhibiting prostaglandin synthesis, a process that is often heightened in endometriosis.

COX-2 and mPGES-1 Inhibitors: Prostaglandin E2 (PGE2) is a significant mediator of inflammation and pain in endometriosis, and its production is driven by enzymes like COX-2, which is overproduced in endometriotic tissue. Selective inhibitors of COX-2 have shown promise in early studies by reducing lesion size and alleviating pain. However, their clinical use is complicated by the potential for cardiovascular side effects, making long-term use problematic. Ongoing research is focused on creating safer COX-2 inhibitors or identifying specific patient groups who might benefit from these treatments with minimal risk (18).

Another target within the prostaglandin synthesis pathway is the enzyme microsomal prostaglandin E synthase-1 (mPGES-1), which directly produces PGE2. Inhibitors of mPGES-1, such as NS-580 (friluglanstat), are being tested in clinical trials. These inhibitors may provide a more precise approach to managing pain in endometriosis by reducing PGE2 production without impacting other prostaglandins that have protective roles. NS-580 has shown encouraging results in early studies for reducing pain and potentially slowing the progression of endometriotic lesions. Current clinical trials are focused on finding the optimal dosing that maximizes therapeutic benefits while minimizing side effects (18).

CGRP Pathway and Repurposed Migraine Medications: Another innovative strategy for pain management in endometriosis involves repurposing drugs originally designed for migraine treatment. Research has revealed common molecular pathways between endometriosis and other chronic pain conditions like migraines, particularly involving the calcitonin gene-related peptide (CGRP) pathway. CGRP, a neuropeptide involved in transmitting pain signals, is found in nerve fibers within endometriotic lesions. By targeting the CGRP pathway, it may be possible to mitigate pain associated with endometriosis.

CGRP receptor inhibitors, such as monoclonal antibodies and small molecule inhibitors (e.g., atogepant), are currently under investigation for their ability to relieve endometriosis-related pain. These drugs block the receptor to which CGRP binds, reducing inflammation and pain transmission in the nervous system. Given that these drugs are already approved for migraine treatment, their known safety profiles could accelerate their adoption for managing pain in endometriosis, offering a non-hormonal treatment option for patients (18).

Alternative and Supportive Therapies for Endometriosis Management

In recent years, alternative and supportive therapies have gained attention as potential options for managing endometriosis, particularly in alleviating the chronic pain often associated with the condition. These methods focus on dietary changes, physical therapies, and complementary medicine practices.

Dietary Interventions and Supplements: There is increasing interest in the role of diet and supplements in managing endometriosis-related pain. While the evidence remains limited, certain vitamins, such as B1, B6, and D, are thought to help manage pain (34,35). Additionally, dietary changes that promote a healthy gut microbiome, such as adopting a low-FODMAP diet, may reduce gastrointestinal symptoms and inflammation linked to endometriosis (36).

Gut-Microbiota-Brain Axis: The gut-microbiota-brain axis is an emerging area of interest in endometriosis research. An imbalance in gut bacteria, known as dysbiosis, has been associated with increased inflammation and changes in pain perception, both of which are crucial in the development of endometriosis. Modifying gut bacteria through dietary adjustments, probiotics, or antibiotics holds potential for symptom relief, although this approach is still being actively researched. Additionally, the interaction between gut bacteria and estrogen metabolism may impact the growth and persistence of endometriotic lesions (18).

Complementary Therapies: Complementary therapies such as acupuncture and electrotherapy have shown potential in reducing endometriosis-related pain. Acupuncture, for example, has been found to decrease pelvic pain by stimulating the body's natural pain control mechanisms (37). However, recommendations for its use vary, with some guidelines supporting its effectiveness while others remain skeptical (8). Transcutaneous Electrical Nerve Stimulation (TENS) has also shown promise in reducing chronic pelvic pain and enhancing the quality of life in women with deep endometriosis (37).

Conclusions

This review focuses on recent developments in the treatment of endometriosis, a complex and chronic condition that significantly impacts the quality of life for many women. While traditional therapies, such as hormonal treatments like progestins, GnRH agonists, and combined oral contraceptives, remain central to managing endometriosis, they often come with considerable side effects and may not fully alleviate symptom (8). This has led to the exploration of new therapeutic approaches.

One of the key findings discussed in this review is the increasing importance of novel treatments targeting specific molecular pathways involved in endometriosis. Aromatase Inhibitors (AIs) have emerged as a promising option, particularly for those who do not respond well to standard hormonal therapies. By reducing local estrogen production in endometriotic lesions, AIs help relieve pain and address symptoms such as gastrointestinal and urinary issues (23), though they are currently considered a second-line treatment due to potential side effects (8).

The review also highlights the benefits of GnRH receptor antagonists, such as Elagolix, which offer advantages over traditional GnRH agonists by providing faster symptom relief and reducing the risk of side effects associated with estrogen suppression (16). These antagonists represent a valuable option for patients needing a more customized treatment approach.

Selective Progesterone Receptor Modulators (SPRMs) and Selective Estrogen Receptor Modulators (SERMs) are additional therapeutic options under investigation. Although SPRMs like Vilaprisan initially showed promise, their development was halted due to safety concerns. However, research into safer and more effective modulators continues. Similarly, SERMs such as Bazedoxifene show potential in inhibiting the growth of endometriotic lesions while preserving the positive effects of estrogen on bone health (16).

The review also emphasizes the potential of targeting interleukins and cytokines involved in the inflammatory processes of endometriosis. Emerging therapies, including IL-8 inhibitors and other cytokine-targeted treatments, show promise in reducing inflammation and pain associated with the disease (31).

Beyond pharmacological treatments, the review highlights innovative approaches to pain management, such as COX-2 and mPGES-1 inhibitors, which aim to reduce prostaglandin synthesis—a key factor in inflammation and pain in endometriosis. Additionally, the repurposing of migraine medications that target the CGRP pathway offers a novel, non-hormonal approach to managing endometriosis-related pain (18).

Finally, the review discusses the growing interest in alternative and supportive therapies, including dietary interventions (34–36), supplements, and complementary treatments such as acupuncture and electrotherapy (8). Although these methods are still being studied, they provide additional options for managing symptoms and improving the quality of life for patients.

In summary, the latest advancements in endometriosis research and treatment offer significant potential for improving patient care. By targeting specific molecular pathways and

exploring new therapeutic strategies, these developments could lead to more effective and individualized treatments, ultimately reducing the impact of this challenging condition on women's health and well-being.

Disclosure

Author's contribution

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Bibliography

1. Becker K, Heinemann K, Imthurn B, Marions L, Moehner S, Gerlinger C, i in. Real world data on symptomology and diagnostic approaches of 27,840 women living with endometriosis. Sci Rep. 14 październik 2021;11(1):20404.

2. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 10 marzec 2014;2014(3):CD009590.

3. França PR de C, Lontra ACP, Fernandes PD. Endometriosis: A Disease with Few Direct Treatment Options. Molecules. 23 czerwiec 2022;27(13):4034.

4. Hadfield R, Mardon H, Barlow D, Kennedy S. Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK. Hum Reprod. kwiecień 1996;11(4):878–80.

5. Arruda MS, Petta CA, Abrão MS, Benetti-Pinto CL. Time elapsed from onset of symptoms to diagnosis of endometriosis in a cohort study of Brazilian women. Hum Reprod. kwiecień 2003;18(4):756–9.

6. Husby GK, Haugen RS, Moen MH. Diagnostic delay in women with pain and endometriosis. Acta Obstet Gynecol Scand. lipiec 2003;82(7):649–53.

7. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med. 26 marzec 2020;382(13):1244–56.

8. Kalaitzopoulos DR, Samartzis N, Kolovos GN, Mareti E, Samartzis EP, Eberhard M, i in. Treatment of endometriosis: a review with comparison of 8 guidelines. BMC Womens Health. 29 listopad 2021;21(1):397.

9. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat Rev Endocrinol. listopad 2019;15(11):666–82.

10. Velasco I, Rueda J, Acién P. Aromatase expression in endometriotic tissues and cell cultures of patients with endometriosis. Mol Hum Reprod. czerwiec 2006;12(6):377–81.

11. De Almeida Asencio F, Ribeiro HA, Ayrosa Ribeiro P, Malzoni M, Adamyan L, Ussia A, i in. Symptomatic endometriosis developing several years after menopause in the absence of increased circulating estrogen concentrations: a systematic review and seven case reports. Gynecol Surg. grudzień 2019;16(1):3.

12. Javert CT. Pathogenesis of endometriosis based on endometrial homeoplasia, direct extension, exfoliation and implantation, lymphatic and hematogenous metastasis, including five case reports of endometrial tissue in pelvic lymph nodes. Cancer. maj 1949;2(3):399–410.

13. Jerman LF, Hey-Cunningham AJ. The role of the lymphatic system in endometriosis: a comprehensive review of the literature. Biol Reprod. marzec 2015;92(3):64.

14. Lu Z, Zhang W, Jiang S, Zou J, Li Y. Effect of oxygen tensions on the proliferation and angiogenesis of endometriosis heterograft in severe combined immunodeficiency mice. Fertil Steril. luty 2014;101(2):568–76.

15. Vercellini P, Crosignani P, Somigliana E, Viganò P, Buggio L, Bolis G, i in. The „incessant menstruation" hypothesis: a mechanistic ovarian cancer model with implications for prevention. Hum Reprod. wrzesień 2011;26(9):2262–73.

16. Shi J, Tan X, Feng G, Zhuo Y, Jiang Z, Banda S, i in. Research advances in drug therapy of endometriosis. Front Pharmacol. 21 czerwiec 2023;14:1199010.

17. Buggio L, Somigliana E, Barbara G, Frattaruolo MP, Vercellini P. Oral and depot progestin therapy for endometriosis: towards a personalized medicine. Expert Opin Pharmacother. październik 2017;18(15):1569–81.

18. Griffiths MJ, Horne AW, Gibson DA, Roberts N, Saunders PTK. Endometriosis: recent advances that could accelerate diagnosis and improve care. Trends Mol Med. 10 lipiec 2024;S1471-4914(24)00166-7.

19. Working group of ESGE, ESHRE and WES. Recommendations for the surgical treatment of endometriosis Part 2: deep endometriosis †‡¶. Facts Views Vis Obgyn. 27 marzec 2020;11(4):269–97.

20. Li XY, Chao XP, Leng JH, Zhang W, Zhang JJ, Dai Y, i in. Risk factors for postoperative recurrence of ovarian endometriosis: long-term follow-up of 358 women. J Ovarian Res. 30 sierpień 2019;12(1):79.

21. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. wrzesień 2012;98(3):511–9.

22. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis. Fertil Steril. grudzień 2012;98(6):1370–9.

23. Ferrero S, Evangelisti G, Barra F. Current and emerging treatment options for endometriosis. Expert Opin Pharmacother. lipiec 2018;19(10):1109–25.

24. Polyzos NP, Fatemi HM, Zavos A, Grimbizis G, Kyrou D, Velasco JG, i in. Aromatase inhibitors in post-menopausal endometriosis. Reprod Biol Endocrinol. 21 czerwiec 2011;9:90.

25. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, i in. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med. 6 lipiec 2017;377(1):28–40.

26. Klingmüller D, Schepke M, Enzweiler C, Bidlingmaier F. Hormonal responses to the new potent GnRH antagonist Cetrorelix. Acta Endocrinologica. styczeń 1993;128(1):15–8.

27. Ford MR, Turner MJ, Wood C, Soutter WP. Endometriosis developing during tamoxifen therapy. Am J Obstet Gynecol. maj 1988;158(5):1119.

28. Harada T, Ohta I, Endo Y, Sunada H, Noma H, Taniguchi F. SR-16234, a Novel Selective Estrogen Receptor Modulator for Pain Symptoms with Endometriosis: An Open-label Clinical Trial. Yonago Acta Med. grudzień 2017;60(4):227–33.

29. Pellicer N, Galliano D, Herraiz S, Bagger YZ, Arce JC, Pellicer A. Use of dopamine agonists to target angiogenesis in women with endometriosis. Hum Reprod. 18 marzec 2021;36(4):850–8.

30. Yarmolinskaya M, Suslova E, Tkachenko N, Molotkov A, Kogan I. Dopamine agonists as genital endometriosis target therapy. Gynecol Endocrinol. 2020;36(sup1):7–11.

31. Nishimoto-Kakiuchi A, Sato I, Nakano K, Ohmori H, Kayukawa Y, Tanimura H, i in. A long-acting anti-IL-8 antibody improves inflammation and fibrosis in endometriosis. Sci Transl Med. 22 luty 2023;15(684):eabq5858.

32. Wu Q, Liang Z, Jiang J, Feng X, Liu J, Zhang Z, i in. Macrophages originated IL-33/ST2 inhibits ferroptosis in endometriosis via the ATF3/SLC7A11 axis. Cell Death Dis. 11 październik 2023;14(10):668.

33. El-Zayadi AA, Mohamed SA, Arafa M, Mohammed SM, Zayed A, Abdelhafez MS, i in. Anti-IL-6 receptor monoclonal antibody as a new treatment of endometriosis. Immunol Res. grudzień 2020;68(6):389–97.

34. Kalaitzopoulos DR, Lempesis IG, Athanasaki F, Schizas D, Samartzis EP, Kolibianakis EM, i in. Association between vitamin D and endometriosis: a systematic review. Hormones (Athens). czerwiec 2020;19(2):109–21.

35. Nirgianakis K, Egger K, Kalaitzopoulos DR, Lanz S, Bally L, Mueller MD. Effectiveness of Dietary Interventions in the Treatment of Endometriosis: a Systematic Review. Reprod Sci. styczeń 2022;29(1):26–42.

36. Moore JS, Gibson PR, Perry RE, Burgell RE. Endometriosis in patients with irritable bowel syndrome: Specific symptomatic and demographic profile, and response to the low FODMAP diet. Aust N Z J Obstet Gynaecol. kwiecień 2017;57(2):201–5.

37. Mira TAA, Buen MM, Borges MG, Yela DA, Benetti-Pinto CL. Systematic review and meta-analysis of complementary treatments for women with symptomatic endometriosis. Int J Gynaecol Obstet. październik 2018;143(1):2–9.