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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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ADVANCES IN ENDOMETRIOSIS THERAPY: A REVIEW OF TARGETED THERAPIES, NANOPARTICLES AND STEM CELLS

Magdalena Koss *(MK) (Corresponding Author, Email: kossmagdalena15@gmail.com)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0009-0000-5775-3810

Weronika Ziomek *(WZ)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0000-0002-8788-5299

Elżbieta Bebrysz *(EB)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0009-0003-0801-4175

Jan Palmi *(JP)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0000-0002-4696-0264

Karolina Dębek-Kalinowska *(KD-K)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0000-0001-9931-6002

Piotr Bartnik *(PB)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0009-0002-5771-3127

Jarosław Baran *(JB)*
Independent Public Healthcare Institution of the Ministry of the Interior and Administration in Lublin, Lublin, Poland
ORCID ID: 0009-0004-7781-2741

Ida Dunder *(ID)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0009-0007-9373-823X

Mateusz Biszewski *(MB)*
1st Military Clinical Hospital with the Outpatient Clinic, Lublin, Poland
ORCID ID: 0000-0003-3082-6420

Aleksandra Drabik *(AD)*
Stefan Kardynał Wyszyński Province Specialist Hospital, Lublin, Poland
ORCID ID: 0009-0008-5434-9351

ABSTRACT

Background: Endometriosis is an estrogen-dependent chronic inflammatory disease characterized by the presence of active endometrium outside the uterine cavity, most commonly in the pelvis. It affects an estimated 10-15% of women of childbearing age and is often associated with infertility, chronic pelvic pain, painful menstruation, and dyspareunia. Despite its high prevalence and significant impact on quality of life, the cause of endometriosis remains unclear, and the available treatment methods have many limitations.
Aim: This article aims to review current developments in endometriosis treatment, with a focus on new therapeutic strategies involving targeted therapies, nanoparticles and stem cells.
Methods: An analysis of the latest (2015-2025) literature from databases such as PubMed and Google Scholar was conducted to synthesize the available information. Search terms included combinations of "Endometriosis treatment," "pathogenesis of Endometriosis," "an update on Endometriosis," "new therapeutics in Endometriosis," and "immunotherapy in Endometriosis," "stem cells and the Endometrium."
Results: In recent years, there has been significant progress in developing targeted therapies that modulate specific signaling pathways, hormone receptors, inflammatory cytokines, and angiogenesis within endometrial lesions. Concurrently, the importance of nanotechnology in medicine, particularly in the context of precision drug delivery using nanoparticles, is growing. Additionally, regenerative therapies using stem cells are receiving increasing attention. These therapies offer the potential to repair damaged tissues and modulate the immune response.
Conclusion: Although preliminary studies are promising, the introduction of these innovative therapies requires further multi-center studies and evaluation of safety and cost. The integration of targeted therapies, nanotechnology and stem cells along with modern molecular diagnostics may soon revolutionize the treatment of endometriosis. This will pave the way for more effective and less invasive methods to improve patients' quality of life.

KEYWORDS

Endometriosis, Cell Therapy, Targeted Therapy, Nanoparticles, Stem Cells

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Introduction and Purpose

Recent decades have brought important advances in understanding the pathophysiology of endometriosis, but the disease still poses serious diagnostic and therapeutic challenges. Despite the availability of pharmacological and surgical approaches, the high recurrence rate and limited efficacy of some therapies underscore the need to seek new solutions.

This review article aims to review the most current directions in the development of therapies for endometriosis with a particular focus on the introduction of new therapeutic strategies: using targeted therapies, nanoparticles and stem cells. Drawing from the literature published between 2015 and 2025, this article provides an overview of methods, summarizes clinical results to date, and identifies knowledge gaps that warrant further research. It offers clinicians and researchers a comprehensive yet critical look at the use of targeted therapies, nanoparticles and stem cells in women with endometriosis.

Materials and Methods

This paper reviews recent advancements in endometriosis treatment, with a focus on three modern therapeutic strategies: targeted therapy, nanoparticle use, and stem cell therapy. A literature search was conducted using PubMed, Google Scholar, and ScienceDirect to identify publications from January 2015 to June 2025. The search included combinations of the following terms: "endometriosis treatment," "pathogenesis of endometriosis," "update on endometriosis," "new therapeutics in endometriosis," "immunotherapy in endometriosis," and "stem cells and the endometrium."

Epidemiology and Histology

Endometriosis is a chronic inflammatory disease affecting up to 10% of women of reproductive age. Despite its significant prevalence and impact on patients' quality of life, the causes and development mechanisms remain incompletely understood. Standard treatments, such as hormonal pharmacotherapy and surgery, often prove inadequate, leading to recurrence and side effects. Therefore, there is a growing need for more effective, less invasive, and personalized endometriosis therapies.

Progress in endometriosis treatment has been made by focusing on three modern therapeutic strategies: targeted therapy, nanoparticle use, and stem cell therapy. These methods each represent a new direction in medicine, focusing on the molecular and cellular mechanisms of the disease. Nevertheless, there is a continued need to develop innovative therapeutic approaches, as existing methods still do not fully meet patients' needs, and the high recurrence rate poses a significant clinical challenge.

The etiology of endometriosis is based on the complex interplay of genetic, hormonal, immunological, and environmental factors. However, there is no clear consensus on the mechanisms that initiate the formation and survival of ectopic endometrial tissue outside the uterine cavity. Scientific literature increasingly emphasizes immune system abnormalities, including reduced natural killer (NK) cell cytotoxic activity, as a potential factor enabling the survival of endometrial cells in abnormal locations [1,2]. Nevertheless, it is unclear whether immune dysfunction is a cause or a consequence of the disease [1,2,3].

Symptoms

The clinical manifestations of endometriosis are extremely varied and often difficult to diagnose. They primarily include chronic pelvic pain, painful menstruation (dysmenorrhea), painful intercourse (dyspareunia), painful urination (dysuria), painful bowel movements (dyschezia), and infertility [2]. These symptoms can significantly reduce patients' quality of life, interfere with daily functioning, and increase the risk of psychiatric disorders, such as depression and anxiety [2]. Notably, the severity of pain, rather than the disease itself, has been shown to be most strongly correlated with the deterioration of patients' mental status [1].

Diagnostics

In recent years, progress has been made toward less invasive diagnostic methods. Traditionally, the gold standard for diagnosing endometriosis was laparoscopy with histopathological evaluation. Today, however, imaging modalities such as transvaginal ultrasonography (TVUS) and pelvic magnetic resonance imaging (MRI) play an increasingly important role [9b]. Combining these methods enables an accurate assessment of lesion progression and allows for more precise treatment planning, whether conservative or surgical [1,3,4].

Treatment

The choice between pharmacological and surgical treatment should always be tailored to the individual needs of the patient, her age, her reproductive plans, the location and extent of the lesions, and previous therapeutic methods. In light of current recommendations, it is advisable to use the least invasive surgical procedures that will not unduly burden a woman's fertility [2]. This is because overly aggressive surgery can lead to postoperative complications, including decreased ovarian reserve or the formation of adhesions [1,5].

Treatment of infertility in women with endometriosis remains a particular challenge, especially in cases of deep infiltrating endometriosis (DIE). Deciding whether to surgically treat or proceed with an in vitro fertilization (IVF) procedure requires extreme caution. Although IVF can be effective, it carries the risk of complications such as infections, difficulties in egg retrieval and ovarian abscesses [2]. There are also concerns about the possible progression of peritoneal lesions or hidden forms of ovarian cancer. Nonetheless, current knowledge does not support the need for prophylactic surgery before IVF, and therapeutic decisions should be made together with the patient, taking into account individual clinical and lifestyle factors [1,2,6].

Therapy of endometriosis therefore requires a multidisciplinary approach, in which not only gynecologists, but also specialists in diagnostic imaging, immunology, surgery, reproductive medicine and psychology play a key role [2]. Only a comprehensive, personalized and evidence-based therapeutic strategy offers a chance to improve patients' quality of life and long-term disease control.

Targeted therapies in the treatment of endometriosis

Next-generation hormonal drugs: aromatase inhibitors and GnRH antagonists

Aromatase inhibitors, such as letrozole and anastrozole, reduce local estrogen levels in endometriosis foci by inhibiting endometrial cell proliferation and the process of angiogenesis. In preclinical studies, the combination of an aromatase inhibitor with statins resulted in complete inhibition of neovascularization in foci [7].

Among GnRH antagonists, oral Elagolix is the first drug in this class approved for clinical use in the treatment of endometriosis pain (Food and Drug Administration, 2018). The drug's efficacy was confirmed in two large, randomized phase III studies of Elaris EM-I and Elaris EM-II involving a total of 1,686 women with moderate to severe endometriosis pain [8,9]. After 3 months of treatment, significant reductions in dysmenorrhea (46% at 150 mg once/day and 72-76% at 200 mg twice/day vs 20-23% placebo) and post-menstrual pain (50-55% and 54-58% vs ~36% placebo) were achieved [8,9]. Extended studies up to 12 months confirmed the maintenance of the clinical effect and a predictable safety profile, including mainly hypoestrogenic symptoms such as hot flashes and a slight reduction in bone mineral density [10].

Immunomodulatory and anti-inflammatory therapies

Endometriosis is associated with dysfunction of the immune system, including overactivity of neutrophils, macrophages, impaired cytotoxicity of NK cells and deregulation of T- and B-lymphocytes. The cytokine profile is also altered, with increased expression of IL-12, IL-37, TGF-β, among others [8].

Approaches being tested include:

- TNF-α inhibitors (infliximab, etanercept), effective in animal models but with limited efficacy in small clinical trials [7].
- Recombinant r-hTBP-I inhibited the development of endometrial lesions in macaque studies [7].
- SiRNAs against CD47, NK-cell activators, IL-12 and IL-37 cytokines, mast cell stabilizers: all these strategies aim to restore immune homeostasis and inhibit the growth of foci [8].

Therapies targeting immuno checkpoint (ICP) pathways such as PD-1/PD-L1, TIM-3/Gal-9, CTLA-4 or OX40 are of increasing interest. Their overexpression on T, B and NK lymphocytes in endometriosis may promote immunosuppression, and blockade of these receptors potentially restores effector activity and inhibits lesion progression [10].

A significant role is also attributed to miRNAs, e.g., let-7b, miR-125, miR-155 modulate inflammatory processes and lymphocyte function. In macaque models, the use of let-7b led to a reduction in the area of foci [11]. In addition, bentamapimod (an inhibitor of c-Jun N-terminal Kinases) in animal model studies showed a regressive effect against endometrial lesions, without affecting the menstrual cycle [11].

Inhibitors of kinases and signaling pathways

Many studies have focused on inhibiting MAPK/ERK, PI3K/AKT, NF-κB, HIF-1α and MMP-2/-9 pathways, which play key roles in endometrial cell proliferation, invasiveness and angiogenesis [12].

Natural phytoconstituents, such as apigenin, curcumin, genistein, luteolin, show the ability to simultaneously modulate multiple signaling pathways (VEGF-A/VEGFR2, p38MAPK/ERK, PI3K/AKT, NF-κB, HIF-1α, COX-2, IL-1β, TNF-α, MMP-2/9, miRNA, lncRNA). These actions can reduce proliferation, invasion, induce apoptosis of pathological cells, and alleviate pain and inflammation [12,13].

Anti-angiogenic therapies

The process of angiogenesis is essential for the development of endometriosis foci. Preclinical studies have shown that statins (lowastatin, atorvastatin) significantly inhibit vascular formation and endometrial cell proliferation [7].

VEGF inhibitors, COX-2 inhibitors, dopamine agonists and phytoconstituents with antiangiogenic activity reduce the expression of VEGF-A, angiopoietins and VEGFR2, reducing vascular permeability and the intensity of the inflammatory response [12]. Mesenchymal stem cells (MSCs) genetically modified to express endostatin are also an interesting direction. In animal models, they have been shown to reduce lesion vascularization and inhibit disease progression [14].

Summary of targeted therapies

An analysis of the available data indicates that targeted therapies for endometriosis include several complementary approaches that differ in mechanism of action, advancement of research, and place in clinical practice.

New-generation hormonal drugs, such as aromatase inhibitors and GnRH antagonists, are the best-documented group, and elagolix, as the first oral GnRH antagonist approved for the treatment of endometriosis pain, is now a viable therapeutic option. Its efficacy has been confirmed in phase III studies and in long-term observations, which confirm both a sustained analgesic effect and an acceptable safety profile [8,9,10].

Immunomodulatory and anti-inflammatory strategies offer new therapeutic options, focusing on the correction of immune disorders typical of endometriosis. Many of them, including immune checkpoint blockers, miRNAs and siRNAs, or TNF-α inhibitors, are at the stage of preclinical studies or early clinical trials [8,10,11].

Kinase inhibitors and modulators of signaling pathways, as well as anti-angiogenic therapies, are promising, showing strong effects in animal models. They may complement hormonal treatment in the future, especially in combination regimens that could reduce doses of hormonal drugs and limit side effects [12,13,14].

Looking ahead to the next few years, the development of targeted therapies in endometriosis should move toward personalized medicine, based on the identification of molecular and immunological biomarkers, which will allow the selection of treatment to suit the individual patient's profile. This approach will increase the effectiveness of therapy, reduce the risk of side effects and improve the quality of life for women with endometriosis.

Nanoparticles in the treatment of endometriosis

Nanoparticles in the treatment of endometriosis is a modern and promising approach to improve the diagnosis of this disease and precise drug delivery. Traditional treatments, have limited efficacy and risk of recurrence, so the development of nanotechnology in the treatment of endometriosis is particularly important [7,8,15].

Types of carriers

Various types of nanocarriers are used. Polymeric nanoparticles, based on copolymers such as PEG-PCL (polyethyleneglycol-poly(ε-caprolactone)), allow both passive accumulation of drugs at lesion sites due to the effect of increased permeability and retention (EPR effect), and active targeting of receptors overexpressed in endometrial tissue, for example, VEGFR2 (KDR) or EphB4 [7,8]. Magnetic nanoparticles, such as cobalt-doped iron oxides (KDR-MN), are used for magnetic resonance imaging (MRI) and low-invasive thermal therapy, where under the influence of a magnetic field they cause selective heating of disease foci and their destruction [16]. In contrast, gold nanoparticles, including HAuNS nanocapsules and their TNYL-HAuNS modifications, exploit photothermal properties, heating lesions under near-infrared (NIR) light and inducing apoptotic death of endometriotic cells [16,17]. Interfering RNA carrier nanoparticles (siRNAs) combined with cell-penetrating peptides (CPPs), such as PepFect6 or NickFect70, are also playing an increasingly important role, precisely repressing the expression of genes crucial in the pathogenesis of endometriosis, enabling molecular modulation of the disease [7,8,18,19].

Examples of nanoparticle applications

Examples of specific applications of nanoparticle therapy are fascinating. Silicon naphthalocyanine nanoparticles (SiNc-PEG-PCL) allow accurate imaging of lesions and their photothermal ablation after intravenous administration, leading to selective destruction of disease sites with minimal impact on healthy tissues [7]. Another example is the use of polymeric PLGA (polylactide-glycolide) nanoparticles with doxycycline and epigallocatechin gallate (EGCG) encapsulated in them. This combination has shown efficacy in reducing matrix metalloproteinases (MMPs) activity, reducing oxidative stress and inhibiting angiogenesis, as confirmed by studies in mouse models [7]. CPP-carrying siRNA nanoparticles delivering danazol and siRNA simultaneously cause synergistic inhibition of endometriotic cell proliferation and invasion in in vitro cultures, combining suppressive effects at the hormonal and molecular levels [8,18]. In addition, work is underway on polymeric nanomaterials below 100 nm containing dyes capable of generating fluorescence for imaging and heating for cell destruction under NIR light, a step toward clinical applications in humans. Nanoparticles bearing ligands, such as folate (folic acid), that precisely bind to receptors overexpressed on

endometrial cells are also being used in therapy, increasing the efficiency of drug transport and reducing toxicity to healthy tissues [16]. The combination of traditional substances, such as danazol or the modern oral GnRH antagonist Elagolix, with nanoparticle carriers is a promising direction to increase the bioavailability and efficacy of therapies in the future.

Advantages of using nanotechnology

The advantage of using nanotechnology in the treatment of endometriosis is primarily the ability to precisely and selectively deliver drugs to the lesions, increasing their concentration where they are needed while minimizing exposure of healthy tissues to toxic effects. This increases the effectiveness of therapy and reduces side effects. Nanoparticles also improve the quality of imaging of endometriosis foci, allowing better localization of micro-focuses during surgical procedures and imaging techniques, especially near-infrared (NIR) or magnetic resonance imaging (MRI) [7,8]. Moreover, they enable combination therapy, providing diagnostic and therapeutic functions, such as photothermal or magnetic ablation of lesions. Nanocarriers also greatly facilitate the transfer of hydrophobic compounds, such as some photosensitizers, improving their bioavailability without increasing systemic toxicity [7].

Limitations and challenges

Despite its many advantages, the application of nanotechnology in the treatment of endometriosis has significant challenges. To date, most studies have been conducted in animal models and in vitro, requiring confirmation of efficacy and safety in extensive human clinical trials. Technical limitations in the resolution and range of available imaging methods make it difficult to detect all lesions and fully exploit the potential of nanoparticles for diagnosis [7,17]. There is also a need to monitor adverse effects associated with the accumulation of nanomaterials in filtering organs, such as the liver and spleen, which may be associated with toxicity. Additionally, the production and standardization of nanocarriers requires further optimization to ensure reproducibility, biocompatibility and safety of formulations for widespread clinical use [7].

Summary of the use of nanoparticles

In summary, the development of nanotechnology in the treatment and diagnosis of endometriosis is opening up new perspectives for the treatment of the disease. With precise drug delivery, better visualization of lesions and innovative thermal therapy methods, nanoparticles have the potential to significantly improve the effectiveness and comfort of treatment, making therapy less invasive and more targeted. The future of their widespread use, however, depends on further clinical trials, technology development and thorough safety assessment to implement these innovations as part of standard care for patients with endometriosis [7,8,15,16,17,18,19].

Use of stem cells in the treatment of endometriosis

The use of stem cells in the treatment of endometriosis is a novel, comprehensive approach. Mesenchymal stem cells (MSCs), especially endometrial MSCs (eMSCs), which exhibit self-renewal, a wide range of differentiation and immunomodulatory activity, play a special role in this therapy [20,21,22,23].

Sources and characteristics of stem cells

Mesenchymal stem cells can be isolated from various tissues: bone marrow, adipose tissue, placenta and endometrium [21,24]. Of these, endometrial MSCs (eMSCs) are particularly important, as they are naturally involved in the physiological regeneration of the endometrium and play a role in endometrial homeostasis [22,25]. However, in endometriosis, MSCs derived from pathological foci show altered phenotype and function, such as increased expression of genes related to inflammation (IL-6, TNF-α) and angiogenesis (VEGF), which may promote the maintenance and development of endometrial foci outside the uterus [25,26].

It has been shown that MSCs isolated from the endometrium of patients with endometriosis have an increased ability to migrate and proliferate, and show altered interaction with the immune system, which may result in an impaired local immune response and promote implantation of ectopic foci [25]. In addition, endometriosis-associated MSCs may also promote the development of ovarian cancers, particularly clear cell carcinoma, by regulating iron metabolism, highlighting the need for a detailed evaluation of the safety of MSC therapy [23,26,27].

Mechanisms of therapeutic action of MSCs

The primary mechanism of action of MSCs in the treatment of endometriosis is their potent immunomodulatory ability. MSCs secrete exosomes containing cytokines, miRNAs and other biologically active factors that regulate immune cell functions - suppressing the activity of effector T cells, pro-inflammatory macrophages and inducing the development of regulatory cells, including regulatory B cells (Breg), which suppress the inflammatory response [20, 28]. The role of MSCs in Breg induction is emphasized, which is crucial for restoring immune balance in the pathological tissue environment [20].

In addition, MSCs exhibit potent anti-angiogenic activity, which is essential in inhibiting the development of new blood vessels that nourish endometrial foci and promote their growth. MSCs modified to express endostatin have been shown to effectively limit angiogenesis in endometriosis by acting through the miRNA-21-5p/TIMP3/PI3K/Akt/mTOR pathway, leading to inhibition of endometrial cell proliferation and survival [27,29]. MSC exosomes additionally transport factors that inhibit the expression of VEGF and other proangiogenic molecules [27,28].

MSCs promote the regeneration of damaged endometrium by stimulating proliferation and differentiation of intraepithelial cells, improving uterine function and increasing the chance of pregnancy in women with endometriosis [24,30]. MSCs can repair tissue damage by modulating the local microenvironment and improving angiogenesis within the uterus, while reducing inflammation [28].

Preclinical and clinical findings

Studies in animal models have shown that administration of MSCs leads to a reduction in the size and number of endometrial foci, lower levels of pro-inflammatory cytokines (IL-1β, TNF-α), and a decrease in angiogenesis markers such as VEGF and CD31 [21,25]. MSCs show the ability to migrate to sites of inflammation and endometrial foci, where they modulate the immune response through secreted factors and inhibit disease progression [21, 26]. Initial clinical studies and case reports suggest that MSC therapy may improve fertility and reduce pain symptoms in patients with endometriosis, although data are still limited and need to be confirmed in large, controlled trials [24,26]. Protocols for the use of MSCs in women with endometriosis-related infertility have been described, indicating improved endometrial function and increased pregnancy rates after therapy [24].

Challenges and prospects for future research

Despite promising results, MSC therapy in endometriosis faces many challenges. The optimal source of MSCs, methods for their isolation, culture and dosage must be detailed to minimize the risk of side effects, including potential promotion of malignant lesions [25,26,31]. In addition, the long-term safety of the therapy must be thoroughly validated, especially in the context of the demonstrated ability of MSCs to modulate the tumor environment [26,31].

Studies also point to the great potential of MSC exosome-based therapy as a cell-free alternative that can reduce the risk of complications associated with live cell administration while maintaining immunomodulatory and regenerative effects [20, 28, 29]. The development of precise tools for genetic modification of MSCs and exosomes will further optimize therapies, increasing their efficacy and safety [29].

Summary of stem cell applications

In conclusion, the use of mesenchymal stem cells in the treatment of endometriosis is a promising and intensively researched field that may significantly improve the quality of life of patients in the future, especially those with fertility problems. It is crucial to conduct further basic and clinical research to optimize and implement these therapies into everyday medical practice [23].

Future research directions

Over the past two decades, the treatment of endometriosis has undergone a transformation from standard hormonal and surgical therapies to more precise, biologically targeted treatments. This review discusses three key therapeutic strategies: targeted therapies, nanoparticles as drug delivery systems, and stem cell therapies. Although each of the three strategies presents a different approach to treating endometriosis, it is possible that they complement each other. For example, nanoparticles can be used to deliver targeted drugs or factors secreted by stem cells. This approach can increase the effectiveness of therapy and reduce the need for surgical

treatment. It is also possible to integrate molecular therapies with regenerative approaches, creating a model for personalized therapy.

Directions for future research:

1. Randomized phase III clinical trials for targeted therapies and nanotherapeutics.
2. Translational research on the safety and efficacy of stem cells.
3. Identification of predictive and prognostic biomarkers to personalize treatment.
4. Combination therapies: evaluating the synergistic effects of different classes of drugs and technologies.
5. Development of gene and epigenetic therapies, especially using CRISPR and siRNA systems.

Conclusions

Clinical evidence suggests that modern, multidirectional therapeutic strategies, including: targeted therapies, nanoparticle-based systems and the use of mesenchymal stem cells (MSCs), may lead to improved treatment outcomes and quality of life for patients with endometriosis. Targeted therapies allow precise intervention in key molecular pathways involved in proliferation, angiogenesis, inflammation and modulation of the immune response. Initial clinical studies confirm that tyrosine kinase inhibitors, estrogen receptor modulators or monoclonal antibodies can significantly reduce the development of endometrial lesions with less systemic toxicity. Nanotechnology, on the other hand, provides tools for controlled, topical and prolonged drug release, resulting in greater efficacy and reduced side effects. Polymeric, liposomal or gold nanoparticles show the ability to penetrate the peritoneal barrier, increasing the bioavailability of active substances within endometrial lesions. In turn, the use of MSCs, thanks to their immunomodulatory, antiproliferative and regenerative properties, opens new perspectives for endometriosis therapy, especially in the context of reducing chronic inflammation and promoting repair processes in pelvic tissues. The combination of cell therapies with tissue engineering and modern drug carriers may become the foundation of personalized treatment strategies in the future.

Although the results of preclinical studies and early phase clinical trials are promising, the implementation of these innovative approaches requires further multicenter validation, the development of standardized protocols, and long-term safety evaluation. It is also necessary to take into account economic aspects and the availability of new technologies in clinical practice. In the coming years, the integration of targeted therapies, nanotechnology and stem cells, supported by the development of molecular diagnostic tools, may lead to a breakthrough in the treatment of endometriosis. Such advances will offer the chance to create effective, less invasive and sustainable therapeutic solutions that will realistically improve the quality of life for millions of patients around the world.

Disclosure

Author Contributions:

Conceptualization: MK
Methodology: MK, KD-K
Software: JP, PB
Formal analysis: ID, MB, WZ
Investigation: KD-K, EB, AD
Resources: JB, PB, ID, MK
Check: JB, JP, MB
Writing - rough preparation: MK, WZ, MB
Writing - review and editing: EB, JB, ID
Supervision: JP, KD-K, AD
Visualization: PB, EB, WZ
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REFERENCES

1. Zondervan, K. T., Becker, C. M., & Missmer, S. A. (2020). Endometriosis. *The New England journal of medicine*, *382*(13), 1244–1256. https://doi.org/10.1056/NEJMra1810764
2. Troìa, L., & Luisi, S. (2021). An update on Endometriosis: what we know from lab to clinic. *Minerva obstetrics and gynecology*, *73*(3), 273–274. https://doi.org/10.23736/S2724-606X.21.04824-7
3. Mariadas, H., Chen, J. H., & Chen, K. H. (2025). The Molecular and Cellular Mechanisms of Endometriosis: From Basic Pathophysiology to Clinical Implications. *International journal of molecular sciences*, *26*(6), 2458. https://doi.org/10.3390/ijms26062458
4. Wang, P. H., Yang, S. T., Chang, W. H., Liu, C. H., Lee, F. K., & Lee, W. L. (2022). Endometriosis: Part I. Basic concept. *Taiwanese journal of obstetrics & gynecology*, *61*(6), 927–934. https://doi.org/10.1016/j.tjog.2022.08.002
5. Shi, J., Tan, X., Feng, G., Zhuo, Y., Jiang, Z., Banda, S., Wang, L., Zheng, W., Chen, L., Yu, D., & Guo, C. (2023). Research advances in drug therapy of endometriosis. *Frontiers in pharmacology*, *14*, 1199010. https://doi.org/10.3389/fphar.2023.1199010
6. Guo S. W. (2009). Recurrence of endometriosis and its control. *Human reproduction update*, *15*(4), 441–461. https://doi.org/10.1093/humupd/dmp007
7. Barra, F., Laganà, A. S., Casarin, J., Ghezzi, F., Ferro Desideri, L., Scala, C., & Ferrero, S. (2019). Molecular Targets for Endometriosis Therapy: Where We Are and Where We Are Going?. *International journal of fertility & sterility*, *13*(2), 89–92. https://doi.org/10.22074/ijfs.2019.5736
8. Slayden, O., Luo, F., Park, Y., Moses, A. S., Demessie, A. A., Singh, P., Korzun, T., Taratula, O., & Taratula, O. (2024). Targeted nanoparticles for imaging and therapy of endometriosis†. *Biology of reproduction*, *110*(6), 1191–1200. https://doi.org/10.1093/biolre/ioae073
9. Taylor, H. S., Giudice, L. C., Lessey, B. A., Abrao, M. S., Kotarski, J., Archer, D. F., Diamond, M. P., Surrey, E., Johnson, N. P., Watts, N. B., Gallagher, J. C., Simon, J. A., Carr, B. R., Dmowski, W. P., Leyland, N., Rowan, J. P., Duan, W. R., Ng, J., Schwefel, B., Thomas, J. W., … Chwalisz, K. (2017). Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *The New England journal of medicine*, *377*(1), 28–40. https://doi.org/10.1056/NEJMoa1700089
10. Surrey, E., Taylor, H. S., Giudice, L., Lessey, B. A., Abrao, M. S., Archer, D. F., Diamond, M. P., Johnson, N. P., Watts, N. B., Gallagher, J. C., Simon, J. A., Carr, B. R., Dmowski, W. P., Leyland, N., Singh, S. S., Rechberger, T., Agarwal, S. K., Duan, W. R., Schwefel, B., Thomas, J. W., … Chwalisz, K. (2018). Long-Term Outcomes of Elagolix in Women With Endometriosis: Results From Two Extension Studies. *Obstetrics and gynecology*, *132*(1), 147–160. https://doi.org/10.1097/AOG.0000000000002675
11. Kapoor, R., Stratopoulou, C. A., & Dolmans, M. M. (2021). Pathogenesis of Endometriosis: New Insights into Prospective Therapies. *International journal of molecular sciences*, *22*(21), 11700. https://doi.org/10.3390/ijms222111700
12. Brichant, G., Laraki, I., Henry, L., Munaut, C., & Nisolle, M. (2021). New Therapeutics in Endometriosis: A Review of Hormonal, Non-Hormonal, and Non-Coding RNA Treatments. *International journal of molecular sciences*, *22*(19), 10498. https://doi.org/10.3390/ijms221910498
13. Dolmans, M. M., & Donnez, J. (2022). Emerging Drug Targets for Endometriosis. *Biomolecules*, *12*(11), 1654. https://doi.org/10.3390/biom12111654
14. Zhou, C., Feng, M., Chen, Y., Lv, S., Zhang, Y., Chen, J., Zhang, R., & Huang, X. (2023). Unraveling immunotherapeutic targets for endometriosis: a transcriptomic and single-cell analysis. *Frontiers in immunology*, *14*, 1288263. https://doi.org/10.3389/fimmu.2023.1288263
15. Lulseged, B. A., Ramaiyer, M. S., Michel, R., Saad, E. E., Ozpolat, B., & Borahay, M. A. (2024). The Role of Nanomedicine in Benign Gynecologic Disorders. *Molecules (Basel, Switzerland)*, *29*(9), 2095. https://doi.org/10.3390/molecules29092095
16. Friend D. R. (2017). Drug delivery for the treatment of endometriosis and uterine fibroids. *Drug delivery and translational research*, *7*(6), 829–839. https://doi.org/10.1007/s13346-017-0423-2

17. Zhu, S., Zhang, J., Xue, N., Zhu, X., Li, F., Dai, Q., Qing, X., Chen, D., Liu, X., Wei, Z., & Cao, Y. (2023). Highly specific neutrophil-mediated delivery of albumin nanoparticles to ectopic lesion for endometriosis therapy. *Journal of nanobiotechnology*, *21*(1), 81. https://doi.org/10.1186/s12951-023-01831-4
18. Kiisholts, K., Kurrikoff, K., Arukuusk, P., Porosk, L., Peters, M., Salumets, A., & Langel, Ü. (2021). Cell-Penetrating Peptide and siRNA-Mediated Therapeutic Effects on Endometriosis and Cancer In Vitro Models. *Pharmaceutics*, *13*(10), 1618. https://doi.org/10.3390/pharmaceutics13101618
19. Wu, Y., Sun, J., Li, A., & Chen, D. (2018). The promoted delivery of RRM2 siRNA to vascular smooth muscle cells through liposome-polycation-DNA complex conjugated with cell penetrating peptides. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *103*, 982–988. https://doi.org/10.1016/j.biopha.2018.03.068
20. Liu, J., Liu, Q., & Chen, X. (2020). The Immunomodulatory Effects of Mesenchymal Stem Cells on Regulatory B Cells. *Frontiers in immunology*, *11*, 1843. https://doi.org/10.3389/fimmu.2020.01843
21. Varela-Pombo, C., López-Viñas, B., Tustain, S. Q., Maquieira, C. G., Mateos, J., Fafián-Labora, J., & Arufe, M. C. (2025). Therapeutic application of mesenchymal stem cells in endometriosis. *Life sciences*, *379*, 123851. Advance online publication. https://doi.org/10.1016/j.lfs.2025.123851
22. Chen, W., Huang, Y., Han, J., Yu, L., Li, Y., Lu, Z., Li, H., Liu, Z., Shi, C., Duan, F., & Xiao, Y. (2016). Immunomodulatory effects of mesenchymal stromal cells-derived exosome. *Immunologic research*, *64*(4), 831–840. https://doi.org/10.1007/s12026-016-8798-6
23. Cevik, E. C., Mamillapalli, R., & Taylor, H. S. (2025). Stem cells and female reproduction: endometrial physiology, disease and therapy. *Stem cells (Dayton, Ohio)*, *43*(5), sxaf016. https://doi.org/10.1093/stmcls/sxaf016
24. Chatzianagnosti, S., Dermitzakis, I., Theotokis, P., Kousta, E., Mastorakos, G., & Manthou, M. E. (2024). Application of Mesenchymal Stem Cells in Female Infertility Treatment: Protocols and Preliminary Results. *Life (Basel, Switzerland)*, *14*(9), 1161. https://doi.org/10.3390/life14091161
25. Kong, Y., Shao, Y., Ren, C., & Yang, G. (2021). Endometrial stem/progenitor cells and their roles in immunity, clinical application, and endometriosis. *Stem cell research & therapy*, *12*(1), 474. https://doi.org/10.1186/s13287-021-02526-z
26. Varela-Pombo, C., López-Viñas, B., Tustain, S. Q., Maquieira, C. G., Mateos, J., Fafián-Labora, J., & Arufe, M. C. (2025). Therapeutic application of mesenchymal stem cells in endometriosis. *Life sciences*, *379*, 123851. Advance online publication. https://doi.org/10.1016/j.lfs.2025.123851
27. Atiya, H. I., Frisbie, L., Goldfeld, E., Orellana, T., Donnellan, N., Modugno, F., Calderon, M., Watkins, S., Zhang, R., Elishaev, E., Soong, T. R., Vlad, A., & Coffman, L. (2022). Endometriosis-Associated Mesenchymal Stem Cells Support Ovarian Clear Cell Carcinoma through Iron Regulation. *Cancer research*, *82*(24), 4680–4693. https://doi.org/10.1158/0008-5472.CAN-22-1294
28. Esfandyari, S., Chugh, R. M., Park, H. S., Hobeika, E., Ulin, M., & Al-Hendy, A. (2020). Mesenchymal Stem Cells as a Bio Organ for Treatment of Female Infertility. *Cells*, *9*(10), 2253. https://doi.org/10.3390/cells9102253
29. de Miguel-Gómez, L., López-Martínez, S., Francés-Herrero, E., Rodríguez-Eguren, A., Pellicer, A., & Cervelló, I. (2021). Stem Cells and the Endometrium: From the Discovery of Adult Stem Cells to Pre-Clinical Models. *Cells*, *10*(3), 595. https://doi.org/10.3390/cells10030595
30. Cousins, F. L., McKinnon, B. D., Mortlock, S., Fitzgerald, H. C., Zhang, C., Montgomery, G. W., & Gargett, C. E. (2023). New concepts on the etiology of endometriosis. *The journal of obstetrics and gynaecology research*, *49*(4), 1090–1105. https://doi.org/10.1111/jog.15549
31. Cheng, Y., Guo, Q., Cheng, Y., Wang, D., Sun, L., Liang, T., Wang, J., Wu, H., Peng, Z., & Zhang, G. (2025). Endostatin-expressing endometrial mesenchymal stem cells inhibit angiogenesis in endometriosis through the miRNA-21-5p/TIMP3/PI3K/Akt/mTOR pathway. *Stem cells translational medicine*, *14*(2), szae079. https://doi.org/10.1093/stcltm/szae079