Review

Hormonal and Emerging Therapeutic Strategies in Endometriosis: Translating Pathophysiology into Targeted Treatment

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Hormonal and Emerging Therapeutic Strategies in Endometriosis: Translating Pathophysiology into Targeted Treatment

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Abstract

Background/Objectives: Endometriosis is a chronic, estrogen-dependent inflammatory disease affecting approximately 10% of reproductive-age individuals and is associated with pelvic pain, infertility, and reduced quality of life. Despite its high prevalence, diagnosis is often delayed for years and current therapies primarily focus on hormonal suppression rather than disease modification. Recent work has clarified several biological pathways involved in endometriosis, including altered estrogen signaling, immune dysregulation, and neuroangiogenesis. These insights have prompted development of new diagnostic strategies and targeted therapies. This review aims to synthesize current evidence on advances in the diagnosis and treatment of endometriosis and to highlight emerging targeted therapies that may improve patient outcomes. **Methods:** A narrative review was carried out using PubMed, Scopus, and Web of Science, focusing on peer-reviewed work from the last two decades on endometriosis diagnosis and treatment. Clinical trials, systematic reviews, consensus recommendations, and observational studies were included to assemble a broad picture of established care and developing strategies. **Results:** Advances in diagnostic approaches include improvements in imaging modalities, development of candidate biomarkers, and exploration of non-invasive diagnostic tools aimed at reducing diagnostic delay. Therapeutic innovations include oral gonadotropin-releasing hormone (GnRH) antagonists, selective progesterone receptor modulators, aromatase inhibitors, and emerging immunomodulatory and anti-inflammatory treatments targeting key molecular pathways involved in disease progression. These developments reflect a shift toward more individualized and mechanism-based treatment strategies. **Conclusions:** Emerging diagnostic tools and targeted therapies represent promising advances in endometriosis care. Continued research integrating molecular insights with clinical practice may facilitate earlier diagnosis, improve symptom control, and support more personalized treatment approaches for individuals affected by endometriosis.

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1. Introduction

Endometriosis is a chronic inflammatory gynecologic disorder characterized by the presence of endometrial-like glands and stroma outside the uterine cavity. The disease affects approximately 10% of reproductive-age individuals worldwide, and up to 30–50% of patients with chronic pelvic pain [1]. Clinically, endometriosis is associated with dysmenorrhea, dyspareunia, chronic pelvic pain, infertility, and diminished quality of life. Additionally, the disease carries substantial societal costs related to healthcare utilization, reduced productivity, and long-term morbidity [2]. Despite its prevalence and impact, endometriosis remains underdiagnosed and undertreated, with studies estimating an average diagnostic delay of 7–10 years between symptom onset and definitive diagnosis [3]. These challenges highlight the urgent need for improved diagnostic strategies and more effective therapeutic approaches.

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The pathogenesis of endometriosis is complex and multifactorial, involving hormonal, immunologic, and inflammatory mechanisms. Historically, the most widely accepted explanation for disease development has been Sampson's theory of retrograde menstruation, which proposes that endometrial tissue refluxes through the fallopian tubes into the peritoneal cavity during menstruation [4]. While retrograde menstruation occurs in the majority of menstruating individuals, only a subset develop endometriosis, suggesting that additional factors play a role in lesion establishment and persistence [5]. Alternative hypotheses such as coelomic metaplasia, stem cell involvement, and lymphatic or hematogenous dissemination have also been proposed to explain disease occurrence in distant or atypical sites [6]. These competing theories underscore the complexity of endometriosis biology and the ongoing debate regarding its underlying mechanisms.

From a diagnostic perspective, endometriosis has traditionally required laparoscopic visualization, which has contributed significantly to delays in diagnosis. However, growing recognition of the clinical burden of delayed diagnosis has driven efforts to develop noninvasive diagnostic tools, including improved imaging modalities and biomarkers [1]. Advances in transvaginal ultrasound and magnetic resonance imaging have improved detection of deep infiltrating disease, while emerging research on circulating biomarkers, inflammatory mediators, and molecular signatures offers the potential for earlier and less invasive diagnosis [7].

Therapeutic strategies for endometriosis have historically focused on suppressing ovarian hormone production to inhibit ectopic endometrial tissue growth. Conventional treatments include combined hormonal contraceptives, progestins, and gonadotropin-releasing hormone (GnRH) agonists, which aim to reduce estrogen-dependent lesion proliferation [8]. While these therapies can alleviate pain symptoms, they do not cure the disease and are often associated with side effects or symptom recurrence after discontinuation. In recent years, advances in understanding the molecular and inflammatory pathways underlying endometriosis have led to the development of novel therapeutic approaches, including oral GnRH antagonists, selective progesterone receptor modulators, aromatase inhibitors, and potential immunomodulatory or anti-inflammatory agents [9]. These innovations reflect a growing shift toward mechanism-based and individualized treatment strategies.

Given the complexity of endometriosis and the limitations of existing management approaches, there is increasing interest in identifying diagnostic and therapeutic advances that may improve patient outcomes. The purpose of this review is to synthesize current knowledge regarding emerging diagnostic tools and evolving therapeutic strategies in endometriosis. This article evaluates progress in noninvasive diagnostic methods and novel medical therapies that target the underlying pathophysiology of the disease. By integrating insights from clinical and translational research, this review highlights the potential for earlier diagnosis and more personalized therapeutic approaches in the management of endometriosis.

2. Methods

2.1. Study Design

A narrative literature review was performed to summarize recent advances in endometriosis diagnosis and treatment. The review focused on peer-reviewed research examining diagnostic innovations, hormonal and non-hormonal therapies, and emerging translational approaches to endometriosis treatment.

2.2. Literature Search Strategy

A literature search was performed using the electronic databases PubMed/MEDLINE, Scopus, and Web of Science to identify relevant peer-reviewed articles. Searches included publications from January 2000 through March 2026 to capture contemporary developments in endometriosis research. Search terms were developed based on key concepts related to diagnosis and therapeutic advances and included combinations of the following keywords: *endometriosis*, *diagnosis*, *biomarkers*, *imaging*,

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pathophysiology, *hormonal therapy*, *GnRH antagonists*, *aromatase inhibitors*, *immunotherapy*, *inflammation*, and *precision medicine*. Boolean operators (AND/OR) were used to refine search results and identify studies addressing both diagnostic and treatment-related topics.

2.3. Data Extraction and Synthesis

Relevant data from included studies were extracted manually and organized thematically according to major topics in endometriosis research, including disease pathophysiology, diagnostic approaches, and therapeutic innovations. Evidence was summarized descriptively, with priority given to high-quality sources such as systematic reviews, randomized controlled trials, large cohort studies, and consensus guideline statements. Diverging findings and areas of ongoing controversy were also highlighted when relevant to clinical practice or research directions.

3. Results

Emerging evidence highlights several areas of progress in endometriosis research, particularly in the domains of disease mechanisms, non-invasive diagnostics, and emerging medical therapies. Together, this data suggests a gradual shift toward mechanism-based and individualized treatment strategies.

3.1. Advances in Understanding Endometriosis Pathophysiology

Several studies have expanded the understanding of endometriosis as a complex systemic disease characterized by hormonal dysregulation, chronic inflammation, immune dysfunction, and neuroangiogenic signaling. Endometriotic lesions demonstrate altered estrogen metabolism, increased aromatase expression, and resistance to progesterone signaling, all of which contribute to persistent lesion growth and inflammatory activity [9]. This reinforces the concept that endometriosis is an estrogen-dependent inflammatory condition with multiple interacting molecular pathways driving disease progression.

In addition to hormonal dysregulation, growing evidence highlights the role of immune dysfunction in the pathogenesis of endometriosis. Abnormal macrophage activation, altered cytokine signaling, and impaired immune clearance of ectopic endometrial cells have been implicated in lesion establishment and persistence. Furthermore, neuroangiogenic mechanisms have been increasingly recognized as key contributors to chronic pelvic pain, as ectopic lesions promote nerve fiber growth and inflammatory sensitization within affected tissues [8].

More recently, research has also explored the potential role of microbiome alterations in endometriosis development. Dysbiosis of the gut and reproductive tract microbiota has been associated with altered inflammatory signaling and estrogen metabolism, suggesting a possible mechanistic link between microbial composition and disease progression [10]. Although preliminary, this data suggests a potential role for the microbiome in endometriosis pathogenesis.

3.2. Emerging Diagnostic Approaches

Historically, laparoscopic visualization with histologic confirmation has been considered the gold standard for diagnosing endometriosis. However, reliance on surgical diagnosis has contributed to significant delays in recognition and treatment. Clinical trials and guidelines emphasize the growing role of non-invasive diagnostic approaches, particularly imaging and molecular biomarker development [11].

3.3. Imaging Advances

Imaging modalities such as transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) have demonstrated improved sensitivity for detecting deep infiltrating endometriosis and ovarian endometriomas when performed by experienced clinicians. Advances in imaging protocols and standardized reporting systems have significantly enhanced the diagnostic accuracy of non-

 doi:10.20944/preprints202604.0081.v1

invasive evaluation, enabling clinicians to identify complex disease without surgical intervention [7]. Additionally, emerging imaging techniques targeting molecular markers (such as integrin-targeted radiotracers), have shown early promise in identifying both superficial and deep endometriotic lesions [12].

3.4. Biomarker Development

Considerable research has focused on identifying reliable non-invasive biomarkers for endometriosis. Candidates including circulating microRNAs, inflammatory cytokines, and proteomic signatures, have demonstrated diagnostic potential. For example, multi-marker panels combining hormonal, genetic, and immunologic markers have shown improved diagnostic accuracy compared with single biomarkers alone [13].

Despite this preliminary work, no biomarker has yet demonstrated sufficient sensitivity and specificity to replace imaging or surgical diagnosis in routine clinical practice [14,15]. Ongoing multicenter validation studies are therefore needed before these approaches can be widely implemented.

3.5. Advances in Medical Management

3.5.1. Established Hormonal Therapies

Traditional medical management of endometriosis has primarily relied on hormonal suppression to inhibit estrogen-dependent lesion growth. First-line treatments include combined hormonal contraceptives and progestins, which reduce menstrual cycling and inflammatory activity. Gonadotropin-releasing hormone (GnRH) agonists have also been widely used to induce hypoestrogenic states, although their use is often limited by adverse effects such as bone mineral density loss and vasomotor symptoms [8].

3.5.2. Oral GnRH Antagonists

One of the most significant therapeutic advances has been the development of oral GnRH antagonists, which directly suppress gonadotropin release. Agents such as elagolix, relugolix, and linzagolix have demonstrated significant reductions in dysmenorrhea and non-menstrual pelvic pain in randomized clinical trials [16,17].

Long-term extension studies have shown that combination therapy with relugolix plus estrogen-progestin add-back therapy can maintain symptom relief for up to two years while mitigating bone mineral density loss and hypoestrogenic side effects [18]. Similarly, the phase-3 EDELWEISS-3 trial demonstrated that linzagolix significantly reduced pain scores within three months of treatment initiation [19]. Collectively, these studies suggest that oral GnRH antagonists represent an important advancement in the pharmacologic management of endometriosis-associated pain.

3.5.3. Emerging Non-Hormonal Therapies

Beyond hormonal suppression, emerging therapies are increasingly targeting the underlying molecular mechanisms of endometriosis. Treatments currently under evaluation include anti-inflammatory agents, angiogenesis inhibitors, immune-modulating therapies, and metabolic pathway inhibitors. For example, early clinical trials exploring metabolic modulators such as dichloroacetate have demonstrated promising reductions in pelvic pain and improvements in quality of life in patient cohorts [11]. Although these therapies remain experimental, they highlight the growing focus on disease-modifying strategies rather than purely suppressive treatments.

3.6. Emerging Concepts in Precision and Multidisciplinary Management

Emerging literature also emphasizes the need for a more personalized approach to endometriosis care. Endometriosis presents with substantial heterogeneity in lesion location,

 doi:10.20944/preprints202604.0081.v1

symptom severity, and response to therapy. As a result, individualized treatment strategies that integrate symptom profile, reproductive goals, disease subtype, and comorbid pain conditions are increasingly recommended [8].

Multidisciplinary care models incorporating gynecology, pain management, reproductive medicine, physical therapy, and psychological support have also gained attention as an effective strategy for improving long-term patient outcomes. This approach reflects the recognition that endometriosis often involves complex interactions between inflammatory, hormonal, neurologic, and psychosocial factors.

Overall, the reviewed literature demonstrates substantial progress in both the diagnosis and management of endometriosis. Advances in imaging have improved detection of deep infiltrating disease. Parallel work on circulating biomarkers may further reduce reliance on surgical diagnosis. Nevertheless, significant challenges remain, including persistent diagnostic delays, variability in treatment response, and the absence of therapies capable of definitively curing or preventing disease progression. Continued research integrating molecular biology, diagnostic innovation, and targeted therapeutics will be critical for improving outcomes in individuals living with endometriosis.

4. Discussion

This narrative review highlights a rapidly evolving landscape in endometriosis care, characterized by (i) a broadened mechanistic understanding of endometriosis as a chronic, heterogeneous, and often systemic inflammatory disorder, (ii) a shift toward non-invasive diagnosis and standardized imaging-based classification, and (iii) meaningful therapeutic advances alongside continued unmet need for durable, disease-modifying and non-hormonal options. Collectively, the literature supports the working hypothesis that improving outcomes will require moving beyond a "one-size-fits-all" model toward phenotype-informed, mechanism-aligned diagnosis and management [1,8,9].

4.1. Interpreting Advances in Diagnosis: From Surgical Confirmation to Risk-Stratified, Imaging-First Pathways

A central controversy in the field remains whether laparoscopy with histology should be considered the default diagnostic "gold standard," versus an approach that prioritizes clinical assessment and expert imaging to reduce delays and procedural burden. The 2022 ESHRE guideline reflects this transition by challenging routine use of laparoscopy as the universal reference and emphasizing a diagnostic pathway that integrates symptoms, imaging, and individualized decision-making [20]. This pivot has been strengthened by multi-society consensus work recommending standardized, high-quality ultrasound and MRI approaches for non-invasive diagnosis and classification of deep endometriosis [21]. These consensus statements provide practical reporting frameworks intended to improve diagnostic consistency and potentially shorten time-to-diagnosis—an outcome of clear clinical relevance given persistent diagnostic delays described in earlier multi-country studies [3].

In parallel, biomarker research continues to expand, reflecting the hypothesis that a reliable non-invasive test could enable earlier recognition and better triage. However, despite enthusiasm for circulating markers such as microRNAs, current evidence indicates modest reproducibility across studies, likely driven by biological variability, menstrual phase effects, and non-standardized pre-analytic/analytic protocols [22]. Thus, while circulating miRNAs remain promising, the field has not yet achieved a clinically validated biomarker with sufficient accuracy to displace imaging and clinical assessment.

 doi:10.20944/preprints202604.0081.v1

4.2. Therapeutic Advances: Improved Symptom Control, Persistent Gaps in Durability and Disease Modification

Therapeutic innovation is most mature in the domain of ovarian suppression, where oral GnRH antagonists have expanded options for patients with moderate-to-severe pain. Pivotal phase 3 trials demonstrated that elagolix improved dysmenorrhea and nonmenstrual pelvic pain versus placebo [16], and replicate phase 3 trials showed that relugolix combination therapy (with estradiol and norethindrone acetate) significantly reduced endometriosis-associated pain while addressing hypoestrogenic adverse effects through add-back [17]. Similarly, the EDELWEISS 3 phase 3 trial reported clinically meaningful improvements in pain with linzagolix, including an approach using lower-dose therapy without add-back and higher-dose therapy with add-back to balance efficacy and tolerability [19]. Systematic review and network meta-analytic data further support short-term efficacy of oral GnRH antagonists while underscoring dose-dependent side effects (e.g., vasomotor symptoms, bone mineral density changes), reinforcing the practical importance of individualized dosing and add-back strategies [23].

At the same time, limitations still persist: symptom recurrence after discontinuation, variable response across phenotypes, and limited evidence that current medical therapies alter long-term disease trajectory [8,9]. The literature increasingly argues that endometriosis-associated pain is not solely nociceptive from lesions but may involve central sensitization, helping explain refractory pain despite adequate lesion suppression or surgery [24]. This supports a more integrated hypothesis: durable pain improvement may require combined strategies targeting peripheral drivers (lesion activity, inflammation) and central pain processing [24].

4.3. Emerging Directions and Contested Hypotheses: Microbiome, Immunology, and Precision Phenotyping

A particularly active (and controversial) frontier involves the microbiome. Systematic review evidence suggests that endometriosis is associated with altered gut microbiome composition and raises the possibility of microbiome-informed diagnostics or adjunctive therapies [10]. Yet causality remains unresolved: microbiome shifts may be drivers, consequences, or correlates of disease and its treatments. Thus, while microbiome modulation is scientifically compelling, clinical translation requires rigorous longitudinal studies that control for hormones, diet, antibiotics, and comorbidities [10].

Similarly, immunomodulatory and anti-inflammatory strategies remain promising but incompletely validated. The mechanistic rationale (immune dysfunction, inflammation, neuroangiogenesis), has strong support [5,9], but high-quality clinical trial evidence for disease-modifying immunotherapies is still limited, and heterogeneity likely necessitates biomarker-driven selection of candidates most likely to benefit. This aligns with a broader field-wide shift toward precision phenotyping, integrating lesion subtype, symptom profile, fertility goals, comorbid pain syndromes, and potentially molecular signatures.

4.4. Limitations

This review has several limitations. Although a structured search was performed, study selection may be subject to publication and selection bias, and no formal risk-of-bias tool or meta-analysis was applied. Additionally, the strength of evidence varies across individual studies: therapeutic trials for GnRH antagonists are comparatively robust, whereas biomarker and microbiome studies often involve smaller cohorts, methodological heterogeneity, and limited external validation.

4.5. Implications and Future Research

Taken together, contemporary evidence supports a modernized clinical approach. This includes imaging diagnostic pathways consistent with guideline recommendations, expanded hormonal options with oral GnRH antagonists and optimized add-back regimens, and an integrated pain

 doi:10.20944/preprints202604.0081.v1

framework that explicitly addresses central sensitization when symptoms persist. Future priorities should include (i) standardized, multicenter validation of non-invasive biomarkers, (ii) trials comparing imaging-first versus surgery-first diagnostic strategies on patient-centered outcomes, (iii) development of non-hormonal and disease-modifying therapies, and (iv) longitudinal multiomic studies that clarify causality and treatment implications.

5. Conclusion

Endometriosis remains a complex and multifactorial gynecologic disorder that continues to pose significant challenges in both diagnosis and management. Despite affecting a substantial proportion of reproductive-age individuals and contributing to chronic pelvic pain, infertility, and reduced quality of life, delays in diagnosis and limitations of existing treatments persist. Understanding endometriosis pathophysiology including the roles of hormonal dysregulation, inflammation, immune dysfunction, and neuroangiogenesis, have helped reshape current perspectives on the disease and inform the development of emerging diagnostic and therapeutic strategies.

Modern progress in imaging modalities and growing efforts to identify noninvasive biomarkers represent important steps toward reducing diagnostic delays and improving early detection. At the same time, the introduction of novel pharmacologic therapies, particularly oral gonadotropin-releasing hormone antagonists and other targeted treatments, has expanded the therapeutic landscape for patients with endometriosis-associated pain. These advances reflect an increasing shift toward mechanism-based and individualized treatment strategies that aim to address both symptom control and underlying disease processes.

Despite these developments, significant unmet needs remain. Current treatments are largely suppressive rather than curative, and many patients experience symptom recurrence after discontinuation of therapy. In addition, the heterogeneity of disease presentation and response to treatment underscores the need for more personalized approaches to management. Future research should prioritize the identification of reliable noninvasive diagnostic biomarkers, the development of disease-modifying therapies targeting key molecular pathways, and improved strategies for individualized patient care.

Integrating advances in molecular biology, imaging, and targeted therapies may substantially improve how endometriosis is diagnosed and treated. Continued multidisciplinary research and collaboration will be essential to reduce diagnostic delays, improve treatment outcomes, and enhance quality of life for individuals living with this chronic and often debilitating condition.

Data Availability Statement: No new data were created or analyzed in this study.

References

1. Zondervan, K.T.; Becker, C.M.; Missmer, S.A. Endometriosis. *New England Journal of Medicine* **2020**, *382*, 1244–1256, doi:10.1056/NEJMra1810764.
2. Soliman, A.M.; Taylor, H.S.; Bonafede, M.; Nelson, J.K.; Castelli-Haley, J. Incremental Direct and Indirect Cost Burden Attributed to Endometriosis Surgeries in the United States. *Fertil Steril* **2017**, *107*, 1181-1190.e2, doi:10.1016/j.fertnstert.2017.03.020.
3. Nnoaham, K.E.; Hummelshoj, L.; Webster, P.; d'Hooghe, T.; de Cicco Nardone, F.; de Cicco Nardone, C.; Jenkinson, C.; Kennedy, S.H.; Zondervan, K.T.; World Endometriosis Research Foundation Global Study of Women's Health consortium Impact of Endometriosis on Quality of Life and Work Productivity: A Multicenter Study across Ten Countries. *Fertil Steril* **2011**, *96*, 366-373.e8, doi:10.1016/j.fertnstert.2011.05.090.
4. Sampson, J.A. Peritoneal Endometriosis Due to the Menstrual Dissemination of Endometrial Tissue into the Peritoneal Cavity. *American Journal of Obstetrics and Gynecology* **1927**, *14*, 422–469, doi:10.1016/S0002-9378(15)30003-X.
5. Burney, R.O.; Giudice, L.C. Pathogenesis and Pathophysiology of Endometriosis. *Fertil Steril* **2012**, *98*, 511–519, doi:10.1016/j.fertnstert.2012.06.029.

 doi:10.20944/preprints202604.0081.v1

6. Vercellini, P.; Viganò, P.; Somigliana, E.; Fedele, L. Endometriosis: Pathogenesis and Treatment. *Nat Rev Endocrinol* **2014**, *10*, 261–275, doi:10.1038/nrendo.2013.255.
7. Chapron, C.; Marcellin, L.; Borghese, B.; Santulli, P. Rethinking Mechanisms, Diagnosis and Management of Endometriosis. *Nat Rev Endocrinol* **2019**, *15*, 666–682, doi:10.1038/s41574-019-0245-z.
8. Taylor, H.S.; Kotlyar, A.M.; Flores, V.A. Endometriosis Is a Chronic Systemic Disease: Clinical Challenges and Novel Innovations. *Lancet* **2021**, *397*, 839–852, doi:10.1016/S0140-6736(21)00389-5.
9. Bulun, S.E.; Yilmaz, B.D.; Sison, C.; Miyazaki, K.; Bernardi, L.; Liu, S.; Kohlmeier, A.; Yin, P.; Milad, M.; Wei, J. Endometriosis. *Endocr Rev* **2019**, *40*, 1048–1079, doi:10.1210/er.2018-00242.
10. Weber, I.; Sienko, A.; Urban, A.; Szwed, C.; Czajkowski, K.; Basta, P.; Sienko, J. Relationship between the Gut Microbiome and Endometriosis and Its Role in Pathogenesis, Diagnosis, and Treatment: A Systematic Review. *Ginekol Pol* **2023**, doi:10.5603/gpl.97581.
11. Griffiths, M.J.; Horne, A.W.; Gibson, D.A.; Roberts, N.; Saunders, P.T.K. Endometriosis: Recent Advances That Could Accelerate Diagnosis and Improve Care. *Trends Mol Med* **2024**, *30*, 875–889, doi:10.1016/j.molmed.2024.06.008.
12. Napolitano, R.; Speltri, G.; Martini, P.; Porto, F.; Marvelli, L.; Niorettini, A.; Uccelli, L.; Urso, L.; Filippi, L.; Uslu, H.; et al. Molecular Imaging Advances in Endometriosis: The Promise of Radiopharmaceuticals. *Molecules* **2025**, *31*, 93, doi:10.3390/molecules31010093.
13. Anastasiu, C.V.; Moga, M.A.; Elena Neculau, A.; Bălan, A.; Scârneciu, I.; Dragomir, R.M.; Dull, A.-M.; Chicea, L.-M. Biomarkers for the Noninvasive Diagnosis of Endometriosis: State of the Art and Future Perspectives. *Int J Mol Sci* **2020**, *21*, 1750, doi:10.3390/ijms21051750.
14. Nisenblat, V.; Bossuyt, P.M.M.; Shaikh, R.; Farquhar, C.; Jordan, V.; Scheffers, C.S.; Mol, B.W.J.; Johnson, N.; Hull, M.L. Blood Biomarkers for the Non-Invasive Diagnosis of Endometriosis. *Cochrane Database Syst Rev* **2016**, *2016*, CD012179, doi:10.1002/14651858.CD012179.
15. Nisenblat, V.; Bossuyt, P.M.M.; Farquhar, C.; Johnson, N.; Hull, M.L. Imaging Modalities for the Non-Invasive Diagnosis of Endometriosis. *Cochrane Database Syst Rev* **2016**, *2*, CD009591, doi:10.1002/14651858.CD009591.pub2.
16. 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.; et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *New England Journal of Medicine* **2017**, *377*, 28–40, doi:10.1056/NEJMoa1700089.
17. Giudice, L.C.; As-Sanie, S.; Arjona Ferreira, J.C.; Becker, C.M.; Abrao, M.S.; Lessey, B.A.; Brown, E.; Dynowski, K.; Wilk, K.; Li, Y.; et al. Once Daily Oral Relugolix Combination Therapy versus Placebo in Patients with Endometriosis-Associated Pain: Two Replicate Phase 3, Randomised, Double-Blind, Studies (SPIRIT 1 and 2). *Lancet* **2022**, *399*, 2267–2279, doi:10.1016/S0140-6736(22)00622-5.
18. Becker, C.M.; Johnson, N.P.; As-Sanie, S.; Arjona Ferreira, J.C.; Abrao, M.S.; Wilk, K.; Imm, S.J.; Mathur, V.; Perry, J.S.; Wagman, R.B.; et al. Two-Year Efficacy and Safety of Relugolix Combination Therapy in Women with Endometriosis-Associated Pain: SPIRIT Open-Label Extension Study. *Hum Reprod* **2024**, *39*, 526–537, doi:10.1093/humrep/dead263.
19. Donnez, J.; Becker, C.; Taylor, H.; Carmona Herrera, F.; Donnez, O.; Horne, A.; Paszkowski, M.; Petraglia, F.; Renner, S.P.; Patel, A.; et al. Linzagolix Therapy versus a Placebo in Patients with Endometriosis-Associated Pain: A Prospective, Randomized, Double-Blind, Phase 3 Study (EDELWEISS 3). *Hum Reprod* **2024**, *39*, 1208–1221, doi:10.1093/humrep/deae076.
20. Becker, C.M.; Bokor, A.; Heikinheimo, O.; Horne, A.; Jansen, F.; Kiesel, L.; King, K.; Kvaskoff, M.; Nap, A.; Petersen, K.; et al. ESHRE Guideline: Endometriosis†. *Hum Reprod Open* **2022**, *2022*, hoac009, doi:10.1093/hropen/hoac009.
21. Condous, G.; Gerges, B.; Thomassin-Naggara, I.; Becker, C.; Tomassetti, C.; Krentel, H.; van Herendael, B.J.; Malzoni, M.; Abrao, M.S.; Saridogan, E.; et al. Non-Invasive Imaging Techniques for Diagnosis of Pelvic Deep Endometriosis and Endometriosis Classification Systems: An International Consensus Statement. *Ultrasound Obstet Gynecol* **2024**, *64*, 129–144, doi:10.1002/uog.27560.
22. Vanhie, A.; Caron, E.; Vermeersch, E.; O, D.; Tomassetti, C.; Meuleman, C.; Mestdagh, P.; D'Hooghe, T.M. Circulating microRNAs as Non-Invasive Biomarkers in Endometriosis Diagnosis-A Systematic Review. *Biomedicines* **2024**, *12*, 888, doi:10.3390/biomedicines12040888.

 doi:10.20944/preprints202604.0081.v1

23. Xin, L.; Ma, Y.; Ye, M.; Chen, L.; Liu, F.; Hou, Q. Efficacy and Safety of Oral Gonadotropin-Releasing Hormone Antagonists in Moderate-to-Severe Endometriosis-Associated Pain: A Systematic Review and Network Meta-Analysis. *Arch Gynecol Obstet* **2023**, *308*, 1047–1056, doi:10.1007/s00404-022-06862-0.
24. Simpson, G.; Philip, M.; Lucky, T.; Ang, C.; Kathurusinghe, S. A Systematic Review of the Efficacy and Availability of Targeted Treatments for Central Sensitization in Women With Endometriosis. *Clin J Pain* **2022**, *38*, 640–648, doi:10.1097/AJP.0000000000001057.