Recent Therapies for Endometriosis: A Systematic Review

Ananda Putra[1], Raymond Malvin Winata[1], El-Varel Baby Berlianzsa[1], Angelica Isabella Monica Chandra[1], Charles Pauris Manubulu[2], Tiara Namora Tarigan[3], Devanti Octavia Ellyamurti[4], Najmarani Devi Firdaus[5], Dilla Alfinda Risdiana[6]

[1] *Faculty of Medicine, Tarumanagara University, Jakarta, Indonesia*
[2] *Leona Hospital, Kefamenanu, East Nusa Tenggara, Indonesia*
[3] *Enggano DTPK Community Health Center, Bengkulu, Indonesia*
[4] *Faculty of Medicine, Trisakti University, Jakarta, Indonesia*
[5] *Department of Obstetrics and Gynecology, Universitas Muhammadiyah Surakarta, Central Java, Indonesia*
[6] *Bentar Community Health Center, Brebes District Health Office, Brebes, Central Java, Indonesia*

Citation : Putra A, Winata RM, Berlianzsa E-VB, Chandra AIM, Manubulu CP, Tarigan TN, Ellyamurti DO, Firdaus ND, Risdiana DA. Recent Therapies for Endometriosis: A Systematic Review. Medicinus. 2025;13(1):101-108
Keywords: endometriosis; systematic review; therapy; hormonal treatment; surgery
Correspondance : Ananda Putra
E-mail : ananda.406211045@stu.untar.ac.id
Online First : 1 October 2023

Abstract

Background:
Endometriosis is a chronic gynecological disorder characterized by the growth of endometrial tissue outside the uterine cavity. It commonly affects women of reproductive age and is associated with chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. The disease significantly impacts productivity, social functioning, and sexual health, making it one of the leading causes of disability and reduced quality of life among women.
Methods:
This review was conducted through a literature search using databases such as PubMed, ScienceDirect, Google Scholar, and ResearchGate. Articles published between 2016 and 2025 were selected using the keywords endometriosis, hormonal therapy, and non-hormonal therapy. Relevant studies were analyzed, cross-referenced, and evaluated to identify current therapeutic strategies for endometriosis management.
Result:
The management of endometriosis currently includes both hormonal and non-hormonal therapies. Hormonal treatments involve the use of aromatase inhibitors, gonadotropin-releasing hormone (GnRH) analogues, selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs), and dienogest, all aimed at suppressing estrogen production and endometrial growth. Non-hormonal therapies, on the other hand, utilize anti-inflammatory, anti-angiogenic, and pro-apoptotic mechanisms to target the inflammatory cascade that contributes to the pathogenesis of endometriosis. These therapies aim to reduce chronic inflammation, cell proliferation, and pain without interfering with ovulation or fertility.
Conclusions:
Both hormonal and non-hormonal therapies play a crucial role in managing endometriosis. While hormonal therapy remains the mainstay of treatment, non-hormonal approaches show promising results with fewer side effects and greater patient tolerability. However, further clinical studies are required to evaluate their long-term efficacy and safety before they can be widely implemented in clinical settings.

Introduction

Endometriosis is a chronic gynecological disorder characterized by the ectopic growth of endometrial tissue outside the uterine cavity.[1] It predominantly affects women of reproductive age and is associated with chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. The disease exerts a profound impact on physical, psychological, and social well-being, often leading to decreased productivity and impaired quality of life. Its pathophysiology involves complex hormonal, inflammatory, and immunological interactions that contribute to persistent pain and progressive lesion formation.[2–4]

Current management strategies for endometriosis are broadly categorized into hormonal and non-hormonal therapies. Hormonal treatments, such as aromatase inhibitors, gonadotropin-releasing hormone analogues, selective estrogen and progesterone receptor modulators, and dienogest, aim to suppress ovarian estrogen production and inhibit endometrial proliferation.[5,6] In contrast, non-hormonal therapies focus on modulating inflammation, angiogenesis, and apoptosis to alleviate symptoms and prevent recurrence without disrupting ovulation or fertility.[7] These approaches are particularly beneficial for patients seeking long-term symptom control with minimal hormonal side effects.

While hormonal therapy remains the cornerstone of endometriosis management, emerging non-hormonal modalities show promising outcomes in improving pain and functional status. Continued research is essential to validate their long-term efficacy, optimize treatment combinations, and personalize therapy according to disease severity and reproductive goals. This paper aims to explain the latest conservative therapeutic approaches for endometriosis, both hormonal and non-hormonal, and explore their potential for broader clinical application.

Material And Methods

This study employed a systematic review design aimed at identifying and synthesizing recent developments in endometriosis therapy. We followed the PRISMA 2020 guideline.[8] A comprehensive literature search was conducted across four major scientific databases: *PubMed*, *ScienceDirect*, *Google Scholar*, and *ResearchGate*. The search was limited to articles published within the last ten years (2016-2025) to ensure the inclusion of the most current and clinically relevant evidence.

The keywords used in the search strategy included *endometriosis*, *hormonal therapy*, and *non-hormonal therapy*. Only peer-reviewed journal articles written in English and focusing on human studies were selected. Studies discussing the pathophysiology, treatment outcomes, mechanisms of action, and comparative analyses of hormonal versus non-hormonal therapies were included.

All retrieved articles were screened for relevance, and duplicate records were removed. The selected studies were reviewed independently by all authors to ensure objectivity and consistency. Key findings were extracted, organized thematically, and summarized to highlight therapeutic mechanisms, clinical outcomes, and potential implications for practice. Discrepancies in interpretation were resolved through group discussion until consensus was achieved.

Result

This review identified two primary therapeutic domains for the management of endometriosis each addressing distinct aspects of the disease's multifactorial pathophysiology. Hormonal approaches remain the mainstay of treatment, primarily aiming to suppress estrogen-driven proliferation and inflammation within ectopic endometrial tissue.[9,10] Agents such as aromatase inhibitors, GnRH analogues, and progestins (dienogest) demonstrated the most consistent clinical efficacy, reducing pelvic pain, dysmenorrhea, and lesion size. Aromatase inhibitors showed particular benefit in refractory cases by

reducing local estradiol synthesis, while dienogest provided sustained symptom control with minimal systemic effects.[11] The addition of selective estrogen and progesterone receptor modulators (SERMs and SPRMs) represents a newer strategy that fine-tunes receptor activity to inhibit endometrial proliferation while preserving bone and metabolic function, although long-term data remain limited.[12–14]

Non-hormonal therapies offer valuable alternatives and adjuncts for patients who are unsuitable for or intolerant to hormonal suppression. NSAIDs remain widely used for pain control through inhibition of prostaglandin synthesis, though their effects are largely symptomatic.[15,16] Agents targeting angiogenic and oxidative pathways, such as dopamine agonists and resveratrol, provide additional benefits by attenuating VEGF–mediated angiogenesis and inflammatory cytokine release. Emerging evidence also supports the use of statins and vitamin D as modulators of immune and inflammatory responses, demonstrating potential in reducing lesion proliferation and pain intensity.[17,18] Nutritional and microbiome-modulating interventions, including omega-3 fatty acids and probiotics, contribute to symptom relief and systemic immune balance, reflecting a growing trend toward integrated metabolic and immunologic management.[19]

Innovative modalities such as HIFU represent a promising, non-invasive therapeutic frontier. By inducing localized thermal ablation of endometriotic lesions, HIFU has shown significant reductions in pain and lesion volume with minimal adverse events and improved quality of life.[20,21] Collectively, the evidence underscores a paradigm shift in endometriosis management. Such approaches may enhance long-term outcomes, reduce recurrence, and preserve reproductive potential in affected women.

Table 1. Summary of Therapeutic Modalities in Endometriosis Management.

Therapeutic Category	Agent / Subtype	Mechanism of Action	Clinical Outcomes
Hormonal Therapy	Aromatase Inhibitors (Letrozole, Anastrozole)	Inhibit aromatase enzyme; reduce local estrogen synthesis and COX-2 activity	↓ Lesion volume, ↓ PGE2 levels, ↓ pelvic pain
	GnRH Agonists / Antagonists (Leuprolide, Goserelin, Elagolix, Relugolix)	Suppress LH/FSH → hypoestrogenic state → lesion regression	↓ Dysmenorrhea, ↓ Dyspareunia, ↓ Lesion size
	Selective Estrogen Receptor Modulators (SERMs) (Raloxifene, S-16234)	Competitive binding to ERα/ERβ; tissue-specific agonist/antagonist action	↓ Pelvic pain, ↓ Dysmenorrhea, preserved bone density
	Selective Progesterone Receptor Modulators (SPRMs) (Mifepristone, Ulipristal, Asoprisnil)	Modulate PR to inhibit proliferation and prostaglandin production	↓ Endometrial thickness, ↓ Pain intensity
	Progestins (Dienogest)	Suppress gonadotropins; reduce estrogenic stimulation; anti-inflammatory	↓ Pain score, ↓ Lesion recurrence, improved tolerance
Non-Hormonal Therapy	NSAIDs (Celecoxib, Rofecoxib, Valdecoxib)	Inhibit COX enzymes → ↓ prostaglandin synthesis	↓ Pain intensity, ↓ Lesion vascularity
	Dopamine Agonists (Cabergoline, Quinagolide)	Inhibit VEGF-mediated angiogenesis	↓ Lesion volume (up to 70%), ↓ Pain
	Resveratrol	Phytoestrogen; antioxidant; inhibits VEGF, TGF-β, and MMP pathways	↓ Inflammation, ↓ Lesion progression
	Statins (Simvastatin)	Inhibit HMG-CoA reductase; reduce inflammatory gene expression	↓ Dysmenorrhea, ↓ Chronic pelvic pain
	Vitamin D	Immunomodulatory and anti-inflammatory; induces apoptosis	↓ Cytokines, ↓ Pain, improved immune balance
	Omega-3 Fatty Acids	Reduce eicosanoid	↓ Menstrual pain, ↓ PGE2,

Therapeutic Category	Agent / Subtype	Mechanism of Action	Clinical Outcomes
		synthesis; anti-inflammatory	improved QOL
	Probiotics (*Lactobacillus* spp.)	Modulate gut microbiome; reduce systemic inflammation	↓ Dysmenorrhea, ↓ Pelvic pain after 8 weeks
	High-Intensity Focused Ultrasound (HIFU)	Ultrasound-induced thermal ablation of lesions	↓ VAS pain scores, ↓ Lesion size, ↑ QOL

Discussion

In this review of current therapeutic options for endometriosis, hormonal treatments remain fundamentally important due to their robust effect on reducing disease burden and symptom severity. For example, in long-term observational studies, daily administration of Dienogest 2 mg resulted in a reduction of major endometrioma size from a mean of 33.2 mm to 7 mm over 108 months (n=157) with significant improvements in dysmenorrhea, dyspareunia and non-cyclic pelvic pain.[22] A meta-analysis further concluded that dienogest is superior to placebo and comparable to GnRH-agonists in lowering recurrence after endometriosis surgery.[23] These findings validate the therapeutic rationale that targeting estrogenic and proliferative mechanisms yields measurable improvement in lesion morphology and symptomatology.

However, the purely hormonal approach is not without limitations. Suppressive therapies such as GnRH-agonists may induce hypoestrogenic side-effects including reduced bone mineral density and menopausal-type symptoms.[24,25] Non-hormonal strategies therefore play an increasingly vital role, particularly for patients seeking fertility preservation or for whom hormonal suppression is contraindicated. For instance, supplementation with omega-3 fatty acids and vitamin D has shown adjunctive benefit in reducing inflammatory mediators and pain intensity.[26–28] Though quantitative data are less abundant, the growing body of literature supports the inclusion of these treatments as part of a multimodal strategy rather than monotherapy.

The shift toward mechanism-based, non-hormonal therapies is well illustrated by emerging agents such as dopamine agonists (to inhibit VEGF-mediated angiogenesis), statins (for anti-proliferative and anti-inflammatory effects), and microbiome-modulating probiotics.[29,30] While high-intensity focused ultrasound (HIFU) represents a non-invasive procedural option that demonstrated significant VAS pain score reductions (-3.6 for dysmenorrhea, P = 0.004; -2.4 for dyspareunia, P = 0.006) in one phase I pilot, these modalities remain adjunctive and experimental.[31] The clinical implications point to a future where treatments are combined, tailored to patient fertility goals, lesion characteristics, and tolerance.

In moving toward personalized management of endometriosis, integration of hormonal and non-hormonal therapies offers the opportunity to maximize efficacy while minimizing side-effects and preserving reproductive potential. Clinical decision-making should incorporate data such as the amenorrhea rate of 58.3% at 12 weeks rising to 86.4% at 72 weeks with dienogest.[32] Further large-scale, long-term randomized trials are needed to compare combination regimens, evaluate cost-effectiveness, and determine optimal sequencing or layering of therapies.[33] Ultimately, the therapeutic goal shifts from purely symptom suppression to sustained disease modification, improved fertility outcomes, and enhanced quality of life.

Study Limitation

This review is limited by its narrative design and reliance on secondary data from previously published studies, many of which differ in methodology, population size, and outcome measures. The lack of uniform diagnostic criteria and variable follow-up durations may affect comparability between studies. Moreover, most available trials have relatively small sample sizes and short-term endpoints, restricting evaluation of long-term efficacy and safety. Publication bias may also overrepresent positive outcomes. Future meta-analyses and randomized controlled trials with standardized protocols are necessary to validate and refine these findings.

Conclusion

Endometriosis remains a complex, multifactorial condition requiring multifaceted management. Hormonal therapies, particularly dienogest and GnRH modulators, continue to demonstrate the strongest evidence base for symptom reduction and lesion regression. However, non-hormonal options, targeting inflammatory, angiogenic, and immunologic mechanisms, offer promising adjunctive or alternative roles, especially for fertility preservation and long-term disease control. Integrating both therapeutic domains into personalized, evidence-based regimens represents the most effective strategy to improve pain outcomes, enhance quality of life, and reduce recurrence among women affected by endometriosis.

Acknowledgment

None.

References

1. Tsamantioti ES, Mahdy H. Endometriosis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Oct 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK567777/.
2. Cano-Herrera G, Salmun Nehmad S, Ruiz De Chávez Gascón J, Méndez Vionet A, Van Tienhoven XA, Osorio Martínez MF, Muleiro Alvarez M, Vasco Rivero MX, López Torres MF, Barroso Valverde MJ, et al. Endometriosis: A Comprehensive Analysis of the Pathophysiology, Treatment, and Nutritional Aspects, and Its Repercussions on the Quality of Life of Patients. Biomedicines. 2024;12:1476. doi: 10.3390/biomedicines12071476.
3. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. BMJ. 2022;e070750. doi: 10.1136/bmj-2022-070750.
4. Pašalić E, Tambuwala MM, Hromić-Jahjefendić A. Endometriosis: Classification, pathophysiology, and treatment options. Pathology - Research and Practice. 2023;251:154847. doi: 10.1016/j.prp.2023.154847.
5. Gheorghisan-Galateanu AA, Gheorghiu ML. HORMONAL THERAPY IN WOMEN OF REPRODUCTIVE AGE WITH ENDOMETRIOSIS: AN UPDATE. Acta Endocrinol (Buchar). 2019;15:276–281. doi: 10.4183/aeb.2019.276. Cited: in: : PMID: 31508191.
6. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord. 2022;23:333–355. doi: 10.1007/s11154-021-09666-w. Cited: in: : PMID: 34405378.
7. Sanamiri K, Mahdian S, Moini A, Shahhoseini M. Non-Hormonal Therapy for Endometriosis Based on Angiogenesis, Oxidative Stress and Inflammation. Int J Fertil Steril. 2024;18:305–313. doi: 10.22074/ijfs.2024.2012554.1547. Cited: in: : PMID: 39564820.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;n71. doi: 10.1136/bmj.n71.
9. Sadłocha M, Toczek J, Major K, Staniczek J, Stojko R. Endometriosis: Molecular Pathophysiology and Recent Treatment Strategies—Comprehensive Literature Review. Pharmaceuticals. 2024;17:827. doi: 10.3390/ph17070827.
10. Petraglia F, Vannuccini S, Donati C, Jeljeli M, Bourdon M, Chapron C. Endometriosis and comorbidities: molecular mechanisms and clinical implications. Trends in Molecular Medicine. 2025;S1471491425002114. doi: 10.1016/j.molmed.2025.09.002.
11. Mercorio A, Giampaolino P, Romano A, Dällenbach P, Pluchino N. Is intracrinology of endometriosis relevant in clinical practice? A systematic review on estrogen metabolism. Front Endocrinol (Lausanne). 2022;13:950866. doi: 10.3389/fendo.2022.950866. Cited: in: : PMID: 36204107.
12. Chantalat E, Valera M-C, Vaysse C, Noirrit E, Rusidze M, Weyl A, Vergriete K, Buscail E, Lluel P, Fontaine C, et al. Estrogen Receptors and Endometriosis. IJMS. 2020;21:2815. doi: 10.3390/ijms21082815.
13. Tang H, Lin T, Wu M, Tsai S. Progesterone resistance in endometriosis: A pathophysiological perspective and potential treatment alternatives. Reprod Medicine & Biology. 2024;23:e12588. doi: 10.1002/rmb2.12588.
14. Tosti C, Biscione A, Morgante G, Bifulco G, Luisi S, Petraglia F. Hormonal therapy for endometriosis: from molecular research to bedside. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017;209:61–66. doi: 10.1016/j.ejogrb.2016.05.032.
15. Wong RSY. Role of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in Cancer Prevention and Cancer Promotion. Advances in Pharmacological Sciences. 2019;2019:1–10. doi: 10.1155/2019/3418975.
16. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging Dis. 2018;9:143–150. doi: 10.14336/AD.2017.0306. Cited: in: : PMID: 29392089.
17. Khan S, Huda B, Bhurka F, Patnaik R, Banerjee Y. Molecular and Immunomodulatory Mechanisms of Statins in Inflammation and Cancer Therapeutics with

Emphasis on the NF-κB, NLRP3 Inflammasome, and Cytokine Regulatory Axes. IJMS. 2025;26:8429. doi: 10.3390/ijms26178429.
18. Farhangnia P, Noormohammadi M, Delbandi A-A. Vitamin D and reproductive disorders: a comprehensive review with a focus on endometriosis. Reprod Health. 2024;21:61. doi: 10.1186/s12978-024-01797-y. Cited: in: : PMID: 38698459.
19. Barrea L, Verde L, Annunziata G, Chedraui P, Petraglia F, Cucalón G, Camajani E, Caprio M, Gorini S, Iorio GG, et al. Effectiveness of Medical Nutrition Therapy in the Management of Patients with Obesity and Endometriosis: from the Mediterranean Diet To the Ketogenic Diet, Through Supplementation. The Role of the Nutritionist in Clinical Management. Curr Obes Rep. 2025;14:68. doi: 10.1007/s13679-025-00662-8. Cited: in: : PMID: 40920291.
20. Zhang X, Duan H. Effect of high-intensity focused ultrasound ablation on endometriosis of the abdominal wall. Int J Clin Exp Pathol. 2018;11:2118–2124. Cited: in: : PMID: 31938321.
21. Wu S, Liu J, Liu X, Han Y. High-intensity focused ultrasound for endometrial ablation in adenomyosis: a clinical study. Front Med (Lausanne). 2024;11:1332080. doi: 10.3389/fmed.2024.1332080. Cited: in: : PMID: 38576714.
22. Maiorana A, Maranto M, Restivo V, Gerfo DL, Minneci G, Mercurio A, Incandela D. Evaluation of long-term efficacy and safety of dienogest in patients with chronic cyclic pelvic pain associated with endometriosis. Arch Gynecol Obstet. 2024;309:589–597. doi: 10.1007/s00404-023-07271-7. Cited: in: : PMID: 38019280.
23. Muzii L, Di Tucci C, Galati G, Carbone F, Palaia I, Bogani G, Perniola G, Tomao F, Kontopantelis E, Di Donato V. The Efficacy of Dienogest in Reducing Disease and Pain Recurrence After Endometriosis Surgery: a Systematic Review and Meta-Analysis. Reprod Sci. 2023;30:3135–3143. doi: 10.1007/s43032-023-01266-0.
24. Ali M, Raslan M, Ciebiera M, Zaręba K, Al-Hendy A. Current approaches to overcome the side effects of GnRH analogs in the treatment of patients with uterine fibroids. Expert Opin Drug Saf. 2022;21:477–486. doi: 10.1080/14740338.2022.1989409. Cited: in: : PMID: 34612122.
25. Surrey ES. GnRH agonists in the treatment of symptomatic endometriosis: a review. F S Rep. 2023;4:40–45. doi: 10.1016/j.xfre.2022.11.009. Cited: in: : PMID: 37223763.
26. Carballo-Casla A, García-Esquinas E, Banegas JR, Rodríguez-Artalejo F, Ortolá R. Fish consumption, omega-3 fatty acid intake, and risk of pain: the Seniors-ENRICA-1 cohort. Clinical Nutrition. 2022;41:2587–2595. doi: 10.1016/j.clnu.2022.09.007.
27. Jerab D, Blangero F, Da Costa PCT, De Brito Alves JL, Kefi R, Jamoussi H, Morio B, Eljaafari A. Beneficial Effects of Omega-3 Fatty Acids on Obesity and Related Metabolic and Chronic Inflammatory Diseases. Nutrients. 2025;17:1253. doi: 10.3390/nu17071253.
28. Xu B, Liang D, Chen G. Evaluation of the Clinical Outcomes Associated With the Use of Fatty Acids and Vitamin D in Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis. Food Sci Nutr. 2025;13:e70473. doi: 10.1002/fsn3.70473. Cited: in: : PMID: 40692609.
29. Chen F-Y, Wang X, Tang R-Y, Guo Z-X, Deng Y-Z-J, Yu Q. New therapeutic approaches for endometriosis besides hormonal therapy. Chin Med J (Engl). 2019;132:2984–2993. doi: 10.1097/CM9.0000000000000569. Cited: in: : PMID: 31809322.
30. Ramos-Nino ME. Non-Hormonal Strategies in Endometriosis: Targets with Future Clinical Potential. JCM. 2025;14:5091. doi: 10.3390/jcm14145091.
31. Atlihan U, Yavuz O, Ata C, Avsar HA, Erkilinc S. Effects of dienogest treatment on endometrioma-related clinical symptoms and endometrioma size: retrospective cohort study. Front Med. 2025;12:1581661. doi: 10.3389/fmed.2025.1581661.

32. Lee SR, Yi KW, Song JY, Seo SK, Lee D-Y, Cho S, Kim SH. Efficacy and Safety of Long-Term Use of Dienogest in Women With Ovarian Endometrioma. Reprod Sci. 2018;25:341–346. doi: 10.1177/1933719117725820. Cited: in: : PMID: 29161960.
33. Wu W, Tang F, Wang Y, Yang W, Zhao Z, Gao Y, Dong H. Cost-effectiveness analysis of combination therapies involving novel agents for first/second-relapse patients with multiple myeloma: a Markov model approach with calibration techniques. Health Econ Rev. 2025;15:21. doi: 10.1186/s13561-025-00611-0. Cited: in: : PMID: 40088315.

Author's Statement

The authors declared that all the images and figures in this manuscript is/are author's own work and/or has obtained necessary permission to re-use the content from the authors and publisher of respective materials.

(Ananda Putra)